First Principles of Gastroenterology and Hepatology

A. B. R. Thomson and E. A. Shaffer, Editors

First Principles of Gastroenterology and Hepatology

CAPstone (Canadian Academic Publishers Ltd) is a not-for-profit company dedicated to the use of the power of education for the betterment of all persons everywhere.

"The Democratization of Knowledge"

2012

This book is endorsed by *The Canadian Association of Gastroenterology*, and *The Canadian Association for the Study of the Liver*

First Principles of Gastroenterology and Hepatology   A. B. R. Thomson and E. A. Shaffer

First Principles and the CANMED Objectives

Medical expert
The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator
The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, to ask questions in an open-ended manner, and to provide constructive, helpful feedback in a professional and non-intimidating manner.

Collaborator
The participants use the "you have a green consult card" technique of answering questions as fast as they are able, and then to interact with another health professional participant to move forward the discussion and problem solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager
Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost effective management plans.

Health advocate
In the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of investigations and therapeutic alliances upon the patient and their loved ones.

Scholar
By committing to the pre- and post-study requirements, plus the intense three day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the "green consult card", they reinforce their previous learning of the importance of collaborating and helping one another to learn.

Professional
The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principals and deductive reasoning. In a safe and supportive setting they learn to seek and accept advice, to acknowledge awareness of personal limitations, and to give and take 360^0 feedback.

Knowledge
 The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the basics of the design of clinical research studies to provide an evidence-based approach, the designing of clinical research studies to provide an evidence-based approach, the relevance of their management plans being patient-focused, and the need to add "compassionate" to the Three C's of Medical Practice: competent, caring and compassionate.

- -

"They may forget what you said, but they will never forget how you made them feel."

Carl W. Buechner, on teaching.

"With competence, care for the patient. With compassion, care about the person."

Alan B. R. Thomson, on being a physician.

Prologue

HREs, better known as, High Risk Examinations. After what is often two decades of study, sacrifice, long hours, dedication, ambition and drive, we who have chosen Internal Medicine, and possibly through this a subspecialty, have a HRE, the [Boards] Royal College Examinations. We have been evaluated almost daily by the sadly subjective preceptor based assessments, and now we face the fierce, competitive, winner-take-all objective testing through multiple choice questions (MCQs), and for some the equally challenging OSCE, the objective standardized clinical examination. Well we know that in the real life of providing competent, caring and compassionate care as physicians, as internists, that a patient is neither a MCQ or an OSCE. These examinations are to be passed, a process with which we may not necessarily agree. Yet this is the game in which we have thus far invested over half of our youthful lives. So let us know the rules, follow the rules, work with the rules, and succeed. So that we may move on to do what we have been trained to do, do what we may long to do, care for our patients.

The process by which we study for clinical examinations is so is different than for the MCQs: not trivia, but an approach to the big picture, with thoughtful and reasoned deduction towards a diagnosis. Not looking for the answer before us, but understanding the subtle aspects of the directed history and focused physical examination, yielding an informed series of hypotheses, a differential diagnosis to direct investigations of the highly sophisticated laboratory and imaging procedures now available to those who can wait, or pay.

This book provides clinically relevant questions of the process of taking a history and performing a physical examination, with sections on Useful background, and where available, evidence-based performance characteristics of the rendering of our clinical skills. Just for fun are included "So you want to be a such-and-such specialist!" to remind us that one if the greatest strengths we can possess to survive in these times, is to smile and even to laugh at ourselves.

Sincerely,

Emeritus Distinguished University Professor, University of Alberta
Adjunct Professor, Western University

<u>Dedication</u>

Without the caring support from our families for our academic work, the meaning of our accomplishments would disappear.

To Cecille Aumont and Kervin Mineault, who taught us what it meant to be a 15th generation Canadien.

Je me souviens.

And to Noah and Zoe (Shaffer Gordon) and Jasper and Macy (Shaffer Nash) who represent the future in this 21st century.

A.B.R. Thomson
E. A. Shaffer

ARE YOU PREPARING FOR EXAMS IN GASTROENTEROLOGY AND HEPATOLOGY?

See the full range of examination preparation and review publications from CAPstone on Amazon.com

Gastroenterology and Hepatology

➢ GI Practice Review, 2nd edition (ISBN: 978-1475219951)

➢ Endoscopy and Diagnostic Imaging Part I (ISBN: 978-1477400579)

➢ Endoscopy and Diagnostic Imaging Part II (ISBN: 978-1477400654)

➢ Scientific Basis for Clinical Practice in Gastroenterology and Hepatology (ISBN: 978-1475226645)

General Internal Medicine

➢ Achieving Excellence in the OSCE. Part I. Cardiology to Nephrology (ISBN: 978-1475283037)

➢ Achieving Excellence in the OSCE. Part II. Neurology to Rheumatology (ISBN: 978-1475276978)

➢ Bits and Bytes for Rounds in Internal Medicine (ISBN: 978-1478295365)

➢ Mastering the Boards and Clinical Examinations. Part I. Cardiology, Endocrinology, Gastroenterology, Hepatology and Nephrology (ISBN: 978-1461024842)

➢ Mastering the Boards and Clinical Examinations. Part II. Neurology to Rheumatology (ISBN: 978-1478392736)

Table of Contents

Chapter 1: Common Symptoms and Signs in Gastroenterology

N. Saloojee

With sections authored by:
R.F. Bursey, M.C. Champion, C. Dube, J.M. Fardy, S. Grégoire,
D.G. MacIntosh, D.G. Patel, A. Rostom, N. Saloojee, L.J. Scully,
A.S.C. Sekar, W.G. Thompson and J.M. Watters

1. Introduction / *N.Saloojee, W.G. Thompson and C. Dubé*

Gastrointestinal (GI) symptoms and disease are extremely common in the general population. GI symptoms and disease will be encountered by all physicians, regardless of specialty. It is therefore important for all physicians to have a framework to approach common GI complaints.

Especially in persons with GI symptoms, taking an accurate history is the key to diagnosis and effective management. In taking the history, the first priority is not to miss serious disease, for example GI malignancy. So called "alarm symptoms" need to be sought out. Dysphagia, GI bleeding, significant weight loss, fever and pain waking the patient from sleep are examples of alarm symptoms that should prompt rapid investigation to exclude a serious GI disorder.

It is important to recognize that GI symptoms may indicate organic disease or functional disease. Organic disease refers to a well defined disorder (eg peptic ulcer disease, inflammatory bowel disease, or malignancy). Patients with functional GI disorders are more common. They have symptoms, but no objective abnormality on physical examination or diagnostic testing. The most common such disorders are irritable bowel syndrome (IBS) and functional dyspepsia (FD). The carefully taken history is often helpful in distinguishing organic from functional disease.

A good interview will include an accurate description of the symptom. This will include time of onset, location, duration, character, and radiation. Aggravating or relieving factors (eg eating or defecation), review of other GI symptoms, past history of GI disease or other illness, prior surgery and family history of GI disease should be sought.

A psychosocial history is important for a number of reasons. Functional disease is more frequent in patients with a history of traumatic life events. In patients with organic disease, anxiety or psychologic stress may worsen symptomatology (eg inflammatory bowel disease). This history is also important in addressing the patient's concerns. A physician cannot adequately address a patient's concerns if he or she does not know what they are.

The following is a synopsis of common GI symptoms. These notes include a description of the symptom, pathophysiologic considerations, important historical features and physical exam findings, and a brief approach to diagnosis and management. Greater detail can be found in later discussions of specific diseases. The final section of this chapter presents an approach to the examination of the abdomen.

2. Globus / *C. Dubé, W.G. Thompson and N. Saloojee*

Globus refers to the sensation of a lump or foreign body in the throat. The sensation may be intermittent or persistent. In a study of healthy volunteers, 45 % of people have experienced this at least once in their lives (1). Globus often occurs during periods of psychologic or emotional stress. Globus is present between meals, and is not food-related. Patients with this symptom swallow normally and without pain. In other words, globus is not associated with dysphagia or odynophagia.

There is no clear etiology for globus. In the majority of cases, no underlying pathology can be identified. In some cases there is an association between globus and the presence of stress, psychiatric disorders, upper esophageal sphincter dysfunction, esophageal dysmotility, or gastroesophageal reflux disease.

Evaluation of this complaint starts with the history. Ensure that the patient does not have dysphagia, odynophagia or other alarm symptoms such as weight loss. Physical examination is generally unrevealing.

Patients with persistent globus should have an ear, nose and throat (ENT) referral. Laryngoscopy is often done to rule out significant ENT pathology. Barium swallow or endoscopy may also be done to exclude significant pathology.

If investigation is negative, globus is best managed with simple reassurance. If globus is severe, a trial of proton pump inhibitor to suppress gastric acid may be given. This is aimed at reducing acid reflux that might contribute to the symptom (2). Endoscopy is often normal in patients with acid reflux. If appropriate, psychiatric consultation may be undertaken.

3. Heartburn and Regurgitation / *C. Dubé, W.G. Thompson and N. Saloojee*
3.1. Description

Heartburn refers to a burning sensation experienced behind the sternum. It is due to reflux of gastric acid into the esophagus. Regurgitation is the effortless return of gastric or esophageal contents into the pharynx without nausea, retching or abdominal contractions. Heartburn and regurgitation often occur concomitantly. They are symptoms of gastroesophageal reflux disease (GERD). Heartburn and regurgitation are common symptoms, with 10-20 % of the general population experiencing this at least once weekly (3). Only a minority of people with these symptoms will seek medical advice.

3.2. History

A number of points are important in taking a history. The sensation of heartburn may radiate to the neck. It is often felt after meals, (especially fatty food, spicy food, caffeine or alcohol). It may be aggravated by lying down, bending over, or straining. Unlike angina, heartburn is not worsened by exercise or physical activity. Ischemic heart disease is often misdiagnosed as GERD, and the physician must take an especially careful history to distinguish between the two common conditions. Misdiagnosing ischemic heart disease for heartburn may have serious consequences for the patient, and medicological issues for the physician.

It is important to note that patients may mean a variety of things when they use the term heartburn. Physicians should closely question patients as to what symptom they have when they say they have heartburn, indigestion, or dyspepsia. Symptoms associated with GERD may include chest pain, epigastric pain, nausea, globus, or less commonly odynophagia. Waterbrash may be associated. Waterbrash is spontaneous hypersalivation, thought to be due to a vagal reflex triggered by excess esophageal acid. Atypical symptoms of reflux can include chronic cough, wheeze or hoarseness.

Dysphagia may be a result from esophageal dysmotility induced by esophageal acid exposure, or it may result from a reflux induced esophageal stricture. Ongoing gastroesophageal reflux is a risk factor for esophageal cancer which can result in dysphagia, weight loss, bleeding or anemia.

The approach to investigation and management of GERD will be reviewed in the chapter "Esophagus."

4. Dysphagia / *A.S.C. Sekar and N. Saloojee*
4.1. Description

Dysphagia means difficulty swallowing. Dysphagia is an alarm symptom requiring prompt evaluation to exclude esophageal malignancy.

It can be classified as oropharyngeal dysphagia or esophageal dysphagia. A good history will distinguish between these two entities.

4.2. Approach to dysphagia

Oropharyngeal dysphagia is also known as "transfer" dysphagia. Patients have difficulty initiating a swallow. They may aspirate such that they cough or choke when they eat. They may have nasal regurgitation of food. Often, oropharyngeal dysphagia occurs in a patient with central nervous system pathology (eg. stroke or amyotrophic lateral sclerosis) or neuromuscular disease (eg myasthenia gravis or dermatomyositis).

Esophageal dysphagia may be due to a mechanical reason causing partial obstruction of the esophagus, or to dysmotility of the esophagus (Table 1). Less commonly, dysphagia results from extrinsic esophageal compression. Patients with esophageal dysphagia describe a sense of food or liquid sticking in the retrosternal area.

Table 1. Causes of Esophageal Dysphagia

Mechanical Lesions	Extrinsic Lesions	Motility Disorders
- Reflux stricture	- Cervical osteophyte	- Achalasia
- Esophageal cancer	- Goitre	- Scleroderma
- Radiation induced stricture	- Mediastinal mass	- Reflux induced dysmotility
- Post surgical anastomotic stricture	- Vascular structure (aberrant subclavian artery)	- Diffuse esophageal spasm
- Stricture post caustic ingestion		- Hypertensive lower esophageal sphincter
- Zenkers Diverticulum		- Nutcracker esophagus
- Esophageal ring or web		

Certain historical points are important in evaluating esophageal dysphagia. Duration and rate of progression should be established. It is important to know if the dysphagia is to solids, liquids or both. A history of heartburn or regurgitation may point to a reflux stricture or reflux-induced esophageal dysmotility. Weight loss, bleeding or anemia could indicate esophageal malignancy. Intermittent dysphagia tends to be seen more in disorders of esophageal motility. A lower esophageal ring (Schatzki's ring) may create intermittent dysphagia. This is because the ring is flimsy, and only sometimes delays passage of food.

Food bolus obstruction may occur in a patient with dysphagia. In this situation, a bolus of food becomes impacted in the esophagus. Patients experience chest discomfort. When they swallow liquid, it is almost immediately regurgitated. The patient will often present to the emergency department and require endoscopic removal of the food bolus. This condition is often seen in persons with eosinophilic esophagitis.

A Zenker's diverticulum is an outpouching immediately above the upper esophageal sphincter. In addition to dysphagia, patients may experience halitosis and aspiration of food retained in the diverticulum.

If a patient is suspected to have oropharyngeal dysphagia, a videofluoroscopy swallowing study (VFSS) can confirm the diagnosis. This is a test in which swallowed contrast material is radiologically visualized. Management of oropharyngeal dysphagia involves treatment of the underlying disorder if possible and dietary modification together with the helpful guidance of a speech language pathologist.

If a patient is suspected to have esophageal dysphagia, evaluation proceeds with either an endoscopy or barium swallow. Barium swallow has the advantage of being noninvasive,

however biopsies cannot be taken. If a stricture is identified at endoscopy (EGD, esophagogastroduodenoscopy), multiple biopsies are necessary to establish whether it is benign or malignant.

When a barium swallow and endoscopy fail to identify any pathology, esophageal manometry may be performed to demonstrate an esophageal motility disorder.

Treatment of esophageal dysphagia depends on the underlying cause. Benign strictures due to reflux are managed with endoscopic dilation and acid suppression in the form of a proton pump inhibitor (PPI). Benign anastomotic strictures, radiation strictures and rings are similarly treated with periodic dilation. Esophageal malignancy is managed through a combination of surgery, radiation, chemotherapy and sometimes with the insertion of a palliative endoscopic stent. A small Zenker's diverticulum is generally followed, whereas larger and more symptomatic lesions may need surgery. Endoscopic management of a large Zenker's diverticulum is possible, but is not done in most centres in Canada.

Achalasia can be managed with periodic Botulinum toxin injections to the lower esophageal sphincter, endoscopic balloon dilation or surgery (myotomy). Treatment of Scleroderma esophagus is mainly with high dose proton pump inhibitor. Reflux dysmotility often responds to proton pump inhibitor. Other esophageal dysmotility disorders are sometimes managed with medication such as nitroglycerin or calcium channel blocker. The effect of such treatment is variable. Further extensive detail of these conditions is given in the chapter "Esophagus."

5. Odynophagia / *N. Saloojee*
5.1. Description
Odynophagia is pain that is felt while swallowing. This symptom is often present with dysphagia. The pain is generally felt in the retrosternal area. Odynophagia is pain, and should be differentiated from the burning discomfort of heartburn.

5.2. Differential diagnosis
Odynophagia implies a break in the mucosa of the esophagus. In an immunocompromised patient the most common cause is infection. The common infections that cause odynophagia are candida, herpes virus and cytomegalovirus. In an immunocompetent patient, an important cause of odynophagia is pill esophagitis. An ingested pill remains in the esophagus and dissolves there, leading to ulceration. This can be a result of not taking the pill with enough liquid, or lying down too soon after taking the pill. Pill esophagitis is a self-limited condition that resolves without specific therapy. Other less common entities that can cause odynophagia include esophageal cancer, radiation esophagitis, and severe reflux esophagitis. Diagnosis rests on endoscopy and mucosal biopsy. Treatment depends on the underlying condition.

6. Dyspepsia / *C. Dubé and N. Saloojee*
6.1. Description
The term, "dyspepsia" refers to chronic or recurrent pain or discomfort centred in the upper abdomen. Patients may refer to this as "indigestion". Various definitions for dyspepsia have been proposed. One such definition is one or more of postprandial fullness, early satiety or epigastric pain. Dyspepsia is a frequent symptom in the general population and, most persons do not seek medical attention.

6.2. Etiology

A variety of conditions can cause dyspepsia. The most common cause is "functional dyspepsia," also known as "non ulcer dyspepsia." Functional dyspepsia is the diagnosis in up to 60 % of cases. In such patients, no anatomic or other abnormality can be documented on upper endoscopy (EGD). The pathophysiology of functional dyspepsia is unclear. It may relate to gastric motor dysfunction, visceral hypersensitivity, psychosocial factors or in some cases it may be associated with gastritis due to an infection with *Helicobacter pylori*.

Peptic ulcer disease and atypical symptoms from gastroesophageal reflux disease (GERD) are the most common organic explanations for dyspepsia. A less common, not to be overlooked cause of dyspepsia is gastric cancer.

6.3. History and Physical

The approach to a patient with dyspepsia begins with a search for so called alarm symptoms. If present, the possibility of significant pathology increases, and investigation should take place in a timely fashion. Alarm symptoms include unintended weight loss, persistent vomiting, progressive dysphagia, odynophagia, otherwise unexplained anemia, gastrointestinal bleeding, and jaundice. Older age also increases the likelihood that dyspepsia is due to organic pathology. It has been suggested that in Canada, an age greater than 50 years be considered an alarm symptom. If the person with dyspepsia is over the age of 50, or if there are alarm symptoms at any age, EGD needs to be performed promptly.

In a young patient with no alarm symptoms, it is very unlikely that dyspepsia will be due to malignancy.

Numerous other disorders can lead to pain in the epigastrium. Careful history will often allow for identification of these. For example, the pain of biliary colic may be present in the epigastric area, but is often in the right upper quadrant as well. Irritable bowel may cause pain in the upper abdomen, but is associated with altered bowel pattern and relief of pain with defecation. As mentioned before, and to emphasize, be certain to take the appropriate history to exclude ischemic heart disease.

Physical examination is generally unhelpful. Epigastric tenderness is a common, but non-specific finding.

6.4. Investigation and Management

Investigation of dyspepsia generally entails bloodwork. This will reveal if the patient is anemic or has abnormal liver enzymes. Patients with alarm symptoms, over the age of 50 even if there are no alarm symptoms, and patients with persistent dyspepsia despite empiric trials of treatment should undergo endoscopy. If resource availability precludes a timely endoscopy, an upper GI series can be done. If a lesion is seen on the upper GI series, a prompt EGD must be arranged.

In younger patients without alarm features, non-invasive testing for *Helicobacter pylori* (*H. pylori* serology or urea breath test) is recommended. If present, *H. pylori* should be treated. The rationale is that if the patient has an ulcer, treating the infection will eliminate the problem of recurrent ulcers. Also, a minority of patents with functional dyspepsia may improve. In young patients without alarm features, another option is an empiric trial of acid suppressive (proton pump inhibitor) or prokinetic (domperidone) therapy. If these approaches fail and dyspepsia persists, endoscopy can be done.

The results of the treatment of functional dyspepsia is disappointing. Some patients may respond to simple reassurance, dietary manipulation, treatment of *H. pylori*, trials of proton pump inhibitor, prokinetic or low dose tricyclic antidepressant (eg. amitryptiline 10-25 mg po once nightly).

7. Nausea and Vomiting / *M.C. Champion and N. Saloojee*
7.1. Description

Nausea is the unpleasant feeling of being about to vomit. Vomiting is the forceful evacuation of stomach contents through the mouth. Vomiting should be differentiated from regurgitation, which is an effortless process. Retching is differentiated from vomiting in that no gastric contents are expelled. Nausea generally precedes vomiting. Vomiting may partially relieve nausea. Vomiting has developed as a defence mechanism, allowing the individual to expel ingested toxins or poisons.

7.2. Mechanism (Figure 1)
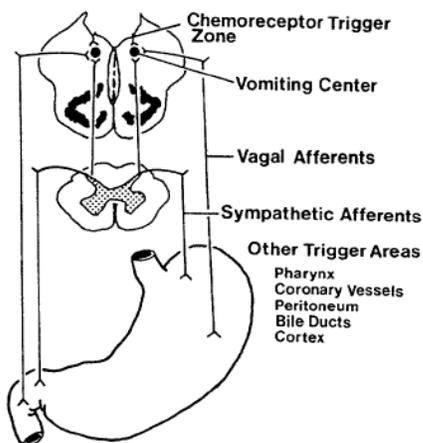
Figure 1. The vomiting center and chemoreceptor trigger zone control vomiting. Peripheral trigger areas send visceral afferent impulses. These excite the vomiting center into action.

Normal motor function of the upper gastrointestinal tract depends on an interplay between the central nervous system and the gut (Figure 1). The neural pathways that mediate nausea are the same as those that mediate vomiting. During nausea, there is gastric relaxation and frequent reflux of proximal duodenal contents into the stomach.

Trigger areas for vomiting exist in the pharynx, cardiac vessels, peritoneum, bile ducts, stomach and cerebral cortex. Excitation of these areas leads to activation of the vomiting centre in the medulla. This is mediated through sympathetic and parasympathetic (vagal) afferents. The chemoreceptor trigger zone exists on the floor of the fourth ventricle on the blood side of the blood-brain barrier. Neurotransmitters, peptides, drugs and toxins may activate the chemoreceptor trigger zone which in turn activates the vomiting centre.

Activation of the vomiting centre leads to forceful abdominal wall contraction, contraction of the pylorus, and relaxation of the lower esophageal sphincter. The glottis closes, and gastric contents are then forcefully expelled.

7.3. History and Differential diagnosis

The differential diagnosis of nausea and vomiting is wide. As alluded to above, nausea and vomiting may be triggered by numerous pathologies arising in many different systems. A good history is therefore critical. Such a history will include inquiry into the timing of the nausea and vomiting. Associated gastrointestinal symptoms such as abdominal pain or diarrhea should be sought. Associated non gastrointestinal symptoms such as headache, chest pain or vertigo are important. As always, obtain the past medical history, past surgical history, family history, and list of medications.

Further questions will suggest themselves as one searches for the specific cause. Table 2 presents a list of more common causes. This list is not exhaustive.

Table 2. Causes of Nausea and Vomiting

- Disorders of the Gut
  - Mechanical Obstruction
  - Gastrointestinal Malignancy
  - Peptic Ulcer Disease
  - Cholecystitis
  - Pancreatitis
  - Hepatitis
  - Gastroenteritis
  - Crohn disease
  - Functional Gastrointestinal disorders
  - Chronic Intestinal Pseudoobstruction
  - Gastroparesis

- CNS disorders
  - Migraine
  - CNS Malignancy
  - Abscess
  - Meningitis
  - Cerebrovascular Accident
  - Hydrocephalus

- Psychiatric disorders
  - Psychogenic vomiting
  - Anorexia Nervosa
  - Bulimia
  - Anxiety / Depression

- Endocrine causes
  - Diabetic Ketoacidosis
  - Hyperthyroidism
  - Addison's disease
  - Hyperparathyroidism
  - Hypoparathyroidism

- Cardiac disease
  - Acute Myocardial Infarction
  - Congestive Heart Failure

- Infections
- Medications, Drug Withdrawal
- Vestibular disorders
- Uremia
- Pregnancy
- Chronic Pain

Given the wide differential, patients with nausea and vomitting should have a complete physical examination. Attention should be paid to signs of volume depletion, and to clues as to the cause of these symptoms.

7.4. Investigation and Management

Investigations ordered depend on the severity of the nausea and vomiting and whether a specific cause is suggested by clinical evaluation. Potential tests include bloodwork, diagnostic imaging of the abdomen and CNS, and endoscopy.

Management rests on treatment of the underlying disorder and correction of fluid and electrolyte imbalance. A number of medications may be used for their antiemetic action. These include antihistamines such as diphenhydramine, phenothiazines, and gastric prokinetics (domperidone, metoclopramide). Domperidone is generally preferred over metoclopramide as it does not cross the blood-brain barrier and therefore does not cause CNS side effects. Ondansetron is a serotonin antagonist used primarily in chemotherapy-induced nausea and vomiting.

8. Anorexia / *M.C. Champion and N. Saloojee*
8.1. Description

Anorexia is a loss of, or lack of appetite. Anorexia is a common and non-specific symptoms. It can be a presenting feature of serious pathology such as malignancy. Alternatively, it may arise from a psychologic or functional disorder.

8.2. History and Physical

A thorough history is needed due to the non-specific nature of this symptom. A calorie count may be helpful to assess the actual intake of food. Any weight loss that has occurred should be documented. Physical examination is often normal.

8.4. Differential Diagnosis

Many diseases feature a loss of appetite. These include gastrointestinal pathology, malignancy, chronic renal failure, and congestive heart failure. Psychiatric illnesses such as depression, anxiety, and anorexia nervosa should be considered.

8.5. Approach to Investigation and Management

Choice of investigations for anorexia depends on the severity of illness and whether specific clues are suggested by history and physical. If no organic disease is discovered, psychiatric problems may be present.

9. Gas and Bloating / *W.G. Thompson and N. Saloojee*
9.1. Description

Patients describing excess gas may be experiencing belching, flatulence, or bloating. Excessive belching or burping is sometimes associated with aerophagia (air swallowing). A degree of aerophagia is physiological, but it may become exaggerated in some patients. Borborygmi is the name given to the noises generated as air and fluid gurgle through the gut. Flatulence is a physiologic phenomenon due to the production of gas by colonic bacteria. Bloating is a perception of abdominal distension. These symptoms often occur together.

9.2. Aerophagia

Commonly, aerophagia is an unwanted but learned habit. Other mechanisms of aerophagia include gum chewing, drinking carbonated drinks, and rapid eating. Stomach gas has the same composition as the atmosphere.

Belching or burping is a physiologic mechanism to relive gastric overdistention with gas. It occurs after a large meal or as a result of aerophagia. Excess belching or burping is rarely a manifestation of significant pathology. It is generally not investigated further unless accompanied by other, more concerning, symptoms.

9.3. Flatulence

Flatulence is a physiologic process. Normally, the gut contains 100 to 200 mL of gas. An average person on a normal diet emits between 500 mL and 1500 mL per day. Excess flatulence is a subjective concern that is defined by the patient's perception. Hydrogen, carbon dioxide, methane and swallowed nitrogen comprise 99% of colonic gas. The remaining 1% consists of trace gases that often have a strong odour. Such gases include hydrogen sulphide, ammonia, skatole, indole and volatile fatty acids. Most emitted gas originates in the colon. Some carbohydrates such as cellulose are not assimilated in the small intestine. They arrive intact in the colon. Here, resident bacteria digest them to produce hydrogen, carbon dioxide, methane and trace gases. Intestinal microbiotica differs from person to person. Some bacteria produce hydrogen, while others consume it. Differing intestinal organisms can be an explanation for excess flatulence.

Excess flatulence is rarely a sign of serious disease. If symptoms such as weight loss or diarrhea are present, investigations to exclude malabsorption may be undertaken. If a patient is concerned about flatus, treatment may include dietary alteration, simethicone (an agent which causes gas bubbles to break), beano (an agent which absorbs gas), or bismuth. On occasion a trial of antibiotic may be given if small bowel bacterial overgrowth is suspected.

9.4. Bloating
9.4.1. Description

Patients experiencing bloating and distention are often convinced that it is due to excess intestinal gas. Despite visible distention in these patients, abdominal x-rays and computerized tomography (CT) show no increase in bowel gas: gas volume in such individuals is not abnormal. Flatulence may temporarily relieve the perception of bloating.

Gut hypersensitivity may explain the sensation of abdominal bloating. The hypersensitive gut feels full with smaller than usual amounts of gas and fluid and abdominal muscles relax to accommodate the perceived distention. Abdominal girth of female irritable bowel syndrome (IBS) patients complaining of distention may increase 3–4 cm over an eight-hour day. CT has demonstrated increased abdominal girth despite unchanged gas content or distribution. There were no corresponding changes in control subjects.

When patients deliberately protrude their abdomens, the configuration is different from when they are bloated, so a conscious mechanism poorly explains increased abdominal girth.

The reality of the phenomenon of bloating is indisputable, however the mechanism remains a mystery.

9.4.2. Clinical Features

Occasionally, bloating occurs in about 30% of adults and is frequent in 10%. Amongst those with functional disorders such as irritable bowel syndrome or functional dyspepsia, the figures are much higher. Bloating is often the most troublesome symptom of these conditions. Often, the abdomen is flat upon awakening, but distends progressively during the day. The distention often disappears with sleep. Patients complain of the need to loosen their clothing.

Bloating may occur quickly, even over just a minute. It is often aggravated by eating and relieved by lying down. Menstrual periods and stress may worsen bloating in some persons.

9.4.3. Differential Diagnosis

When assessing a patient with bloating and visible abdominal distension, the physician should exclude conditions such as ileus, bowel obstruction, ascites, or intrabdominal tumour. Ileus is a condition in which intestinal motility is reduced. The small and large bowel dilate. This can lead to abdominal distention. Ileus can occur due to medication such as narcotics. It is often seen in the postoperative state. A patient with a bowel obstruction will also have a visibly distended abdomen.

The abdomen can be distended by the presence of fluid in the peritoneal cavity. This condition is called ascites. Rarely, a large tumour in the peritoneal cavity can lead to abdominal distention. Generally these conditions can be separated out with a history and physical as other signs and symptoms are present. If necessary, imaging with abdominal X ray or ultrasound is definitive.

On its own, bloating is not a symptom of organic disease, and should not prompt investigation.

10. Constipation / *C. Dubé, W.G. Thompson and N. Saloojee*
10.1. Description

Constipation is also known as obstipation. A precise definition of constipation is elusive due to the variability of what constitutes a normal bowel pattern. Ninety five percent or more of the population have between three movements per day and three movements per week. Some physicians consider that fewer than three movements a week without discomfort or dissatisfaction is normal. Most would agree that hard bowel movements that are difficult to pass constitute constipation even if they occur as often as daily.

The most common terms which patients use to describe constipation are "straining", hard stools" and the " inability to have a bowel movement". Therefore, constipation is a symptom that does not always correlate with infrequent passage of bowel movements.

Constipation is best understood as persistent symptoms of difficult evacuation. This may include straining, stools that are excessively hard, unproductive urges, infrequent bowel movements, or a feeling of incomplete evacuation, often defecation.

10.2. Mechanism

Many conditions can result in constipation. The most common kind of constipation is that associated with irritable bowel syndrome (Table 3). Constipation may be due to primary colonic conditions. Examples are an obstructing colon cancer or idiopathic slow-transit constipation.

Constipation may also be caused by systemic diseases. For example, endocrine disorders (diabetes mellitus, hypothyroidism), metabolic disturbances (hypo- or hypercalcemia), neurologic disorders (multiple sclerosis, Parkinson's disease), muscular disease (systemic sclerosis, myotonic dystrophy), or medications (opiates, anticholinergic agents).

Proper defecation requires normal transit through the proximal colon, an intact gastrocolic response to a meal, and normal mechanisms of defecation. The gastrocolic response is simply an increase in colonic motility triggered by gastric distention. This reflex is responsible for the urge to defecate after a meal. Defecation requires an intact defecation reflex. In this reflex, stool in the rectum triggers an urge to defecate. Coordinated relaxation of the puborectalis and external anal sphincter muscles must occur.

Table 3. Some causes of chronic constipation

- ➤ Primary diseases of the colon
  - o Stricture
  - o Cancer
  - o Anal fissure
  - o Irritable bowel syndrome
  - o Idiopathic slow-transit constipation

- ➤ Pharmacologic
  - o Opiates
  - o Antidepressants
  - o Anticholinergic agents
  - o Calcium channel blockers
  - o Iron
  - o Laxative abuse

- ➤ Pregnancy

- ➤ Pelvic floor dyssynergia

- ➤ Metabolic disturbances
  - o Hypercalcemia
  - o Hypothyroidism
  - o Diabetes mellitus
- ➤ Neurologic and muscular disorders
  - o Parkinson's disease
  - o Spinal cord lesion
  - o Multiple sclerosis
  - o Autonomic neuropathy
  - o Hirschsprung's disease
  - o Systemic sclerosis (Scleroderma)
  - o Myotonic dystrophy

10.3. Important Points on History and Physical Examination

Taking a good dietary history is important to help manage the person with constipation. This involves an assessment of daily fibre intake, fluid consumption and meal patterns. Many constipated patients do not eat breakfast. As mentioned, colonic motility increases after meals as part of the gastrocolic reflex.

Physical activity stimulates colonic motility. Therefore one should inquire about exercise. Physical impairments leading to impaired mobility will contribute to constipation.

The list of medications should be reviewed. A history of prolonged intake of cathartics, often in the form of herbal remedies or teas, should be sought. Prolonged use of stimulant laxatives can sometimes lead to permanent impairment of colonic motility.

Symptoms such as bloating, abdominal pain relieved with defecation, and alternation of constipation with diarrhea should be sought. These symptoms suggest a diagnosis of irritable bowel syndrome. Stress incontinence suggests a problem with pelvic floor musculature. Weight loss or rectal bleeding raise the possibility of an obstructing colon cancer. Some persons with constipation may leak fluid stool around the inspisated stools, leading to "overslow diarrhea."

There may be the presence of abdominal distension or palpable stools, but the physical examination of patients with constipation is generally unreavealing. Digital rectal examination (DRE) is useful to identify fissures or hemorrhoids. These may cause constipation, since the patient tries to avoid pain induced by defecation. Fissures or hemorrhoids may also result from constipation. A lax anal sphincter may sometimes suggest a neurologic disorder. The presence of stools in the rectum on DRE may sometimes suggest an impaired defecation reflex.

10.4. Approach to Diagnosis

Constipation is a common symptom. Many patients, particularly those that are younger or those with milder symptoms will need minimal or no investigation.

If investigation is deemed necessary, bloodwork including hemoglobin, inflammatory markers such as erythrocyte sedimentation rate and c reactive protein, blood sugar, thyroid

function tests and serum calcium may be done. Inflammatory markers may be elevated in persons with Crohn disease. Crohn's is an inflammatory bowel disease which may sometimes lead to colonic stricture. Lower endoscopy with either sigmoidoscopy or colonoscopy may be done to rule out structural lesions such as a colonic stricture, malignancy or anal fissure. Endoscopic testing may also detect melanosis coli, a disorder in which there is hyperpigmentation of the colonic mucosa due to chronic use of laxatives. If a patient is over 40 years of age or if alarm symptoms (such as rectal bleeding or weight loss) are present, colonoscopy would be indicated as opposed to sigmoidoscopy. Sigmoidoscopy does not assess the more proximal colon. Alternate tests to assess the structure of the colon include air contrast barium enema or CT colonography. CT colonography is also known as virtual CT and provides radiologic images of the interior of the colon. This test does not allow for biopsy or other intervention, but may be done if colonoscopy cannot be performed or is not readily available.

Occasionally other tests are done. A gut transit study may be revealing. Twenty radiopaque markers are ingested and daily plain abdominal x-rays are taken. If 80% of the markers have disappeared in five days, the transit time is said to be normal. When the transit time is longer than 5 days, the position of the markers may help distinguish slow colonic transit from an anorectal disorder: if remaining markers are seen throughout the colon, slow colonic transit is present. If remaining markers are all in the rectum, an anorectal disorder is present. Anorectal manometry and defecography, are then required.

10.5. Approach to Management

In the majority of patients, a specific disorder is not diagnosed. In these cases, management includes education as to the great variability of bowel habits among the general population. Reassurance is sometimes all that is required.

Where further intervention is needed, dietary changes can be made. This includes the intake of at least three meals a day and adequate amounts of liquids. While no data proves the efficacy of increased fluid intake, 6 to 8 cups per day of water are often recommended. A high fibre intake can be achieved with increased dietary fibre or a commercial fibre product. This increases stool bulk and frequency of bowel movement. The recommended amount of dietary fibre is 20 to 35 g/day. High doses only cause adverse effects, and are not recommended. Regular exercise is often helpful, as it stimulates colonic motility.

Chronic severe constipation may require the use of osmotic agents such as magnesium, lactulose or polyethylene glycol solution. The long-term use of stimulant laxatives such as bisacodyl or senna should be avoided.

More details about this important and common problem are given in the chapter "Colon".

11. Diarrhea / *W.G. Thompson and N. Saloojee*
11.1. Description

Diarrhea is defined as bowel movements that are too frequent, too loose or both. Three or more bowel movements per day, or a stool weight of over 200 grams / day is generally considered to be abnormal. In clinical practice, stool weight is rarely measured. Diarrhea is frequently accompanied by urgency. It is important to determine if the patient is using the word "diarrhea" when in fact they have fecal incontinence.

11.2. Mechanism

The four mechanisms of diarrhea are osmotic, secretory, inflammatory and rapid transit. In many instances of diarrhea, two or more of these four mechanisms are at work. Therefore, these mechanisms provide a framework for understanding diarrhea, however they are seldom of great help when approaching a patient in clinical practice. In clinical practice, an anatomical approach is much easier and more useful (please see the chapter on Small Intestine).

If the osmotic pressure of intestinal contents is higher than that of the serum, fluid is drawn into the lumen of the intestinal tract and osmotic diarrhea results. This may result from malabsorption of fat (e.g. celiac disease) or of lactose (e.g. in intestinal lactase deficiency). Certain laxatives, such as lactulose and magnesium hydroxide, exert their cathartic effect largely through osmosis. Certain artificial sweeteners, such as sorbitol and mannitol, have a similar effect. Beware of diabetic candies causing diarrhea. Characteristically, osmotic diarrhea ceases when the patient fasts or sleeps.

Secretory diarrhea occurs when there is a net secretion of water into the intestinal lumen. This may occur with bacterial toxins, such as those produced by *E. coli* or *Vibrio cholerae*. It may occur with hormones, such as vasoactive intestinal polypeptide (VIP). Excess VIP is produced by some pancreatic islet cell tumours. In these rare tumours, VIP provokes adenylate cyclase activity in the enterocyte (intestinal epithelial cell). The result is increased cyclic AMP and intestinal secretion. A similar effect may occur as a result of excess bile salts in the colon. Secretory diarrhea does not diminish with fasting, and the patient will be up at night-time to have bowel motion.

Exudative diarrhea results from direct damage to the small or large intestinal mucosa. This interferes with the absorption of sodium salts and water and is complicated by exudation of serum proteins, blood and pus. Infectious or inflammatory disorders of the gut cause this kind of diarrhea.

Acceleration of intestinal transit may result in diarrhea. An example of this is diarrhea related to hyperthyroidism. The rapid flow impairs the ability of the gut to absorb water, resulting in diarrhea.

11.3. Important Points on History and Physical Exam

The duration of diarrhea is important. If diarrhea has been present for less than two weeks, it is categorized as being acute. Acute diarrhea is almost always due to an infection or food poisoning. Chronic diarrhea, defined as lasting over 2 weeks, has many potential etiologies and often requires investigation.

Knowing the volume of diarrhea can provide a clue to the cause. Distal colonic pathology generally leads to a small volume diarrhea. Small bowel or proximal colonic pathology generally leads to a large volume diarrhea. Patients may have difficulty in categorizing the volume of diarrhea, and asking them to describe their stool volume as "little squirts" or "big gushes" may be helpful.

Further history includes knowing the characteristics of the diarrhea, such as frequency and consistency. Associated symptoms such as rectal bleeding, weight loss, and abdominal pain should be elicited. Foul smelling, floating or oily stool may indicate fat malabsorption. The presence of intermittent normal or constipated bowel movements suggests irritable bowel syndrome. A thorough medication history is necessary. Recent antibiotic use is of particular importance since this is a risk factor for clostridium difficile, a common cause of diarrhea. Other questions include travel history, exposure to individuals with diarrhea, and sexual practices

which might lead to immune deficiency (e.g. HIV/AIDS).

There are many causes of diarrhea, some of which are summarized in Table 4. This list is not exhaustive. Each of these causes will suggest further questions to the interviewer. Physical exam is generally more useful in assessing the severity of diarrhea, rather than finding a cause. Volume status is best determined by looking for changes in pulse and blood pressure.

Table 4. Differential Diagnosis of Diarrhea

➤ **Acute Diarrhea**
- o Infection
- o Food Poisoning

  o Initial Presentation of Chronic Diarrhea

➤ **Chronic Diarrhea**

➤ Gastric
- − Dumping syndrome

➤ Pancreas
- − Chronic pancreatitis
- − Islet cell tumours (e.g. VIPoma)

➤ Small intestine
- − Celiac disease
- − Lymphoma
- − Whipple's disease
- − Parasitic infection (ex Giardia lamblia)
- − Bacterial overgrowth
- − Bile salt malabsorption
- − Diabetic Autonomic Neuropathy
- − Short Bowel Syndrome

➤ Drugs
- − Antibiotics
- − Alcohol
- − Laxatives
- − Nonsteroidal anti-inflammatories
- − Sorbitol, fructose
- − Many others

➤ Metabolic/Endocrine
- − Hyperthyroidism
- − Addison's disease
- − Diabetes
- − Carcinoid syndrome

➤ Large bowel
- − Villous adenoma / Colon cancer
- − Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- − Irritable bowel
- − Functional diarrhea
- − HIV related infections

11.5. Investigation and Management

Acute diarrhea is self-limiting and may not need investigation. If it is more severe, investigation focuses on searching for an infection through stool tests for culture and sensitivity, ova and parasites and *Clostridium difficile*toxin. Viral studies are important in infants.

As noted, the differential diagnosis of chronic diarrhea is long. Testing will vary depending on the individual case, case, but may include bloodwork, stool testing, gastroscopy and small bowel biopsy, colonoscopy and biopsy, and imaging of the small bowel and abdomen.

Practice points
- o Gastrointestinal complaints are common in the general population
- o Fear of underlying malignancy is a common reason for a complaint to come to medical attention

- o Functional GI disorders are common
- o Thorough and careful history-taking is crucial in gastroenterology. This includes family history for such disorders as malignancy, celiac disease, IBD, and liver disease
- o Alarm symptoms such as weight loss, bleeding, dysphagia should lead to prompt investigation for organic pathology
- o The history may lead to a differential diagnosis (increasing pre-test probability of a physical finding), so that additional care and the use of supplemental tests will be used on physical examination
- o Physical examination involves much more than just the abdomen. It should include a thorough examination of all parts of the body, looking for extraintestinal signs such as may occur in persons with cirrhosis, celiac disease, inflammatory bowel disease, and nutritional deficiencies

12. Malnutrition / *D.G. Patel*

12.1. Description

Nutrition may be defined as the process by which an organism utilizes food. This complex process involves ingestion, digestion, absorption, transport, utilization and excretion. Any alteration in one or many of these factors can produce malnutrition. Globally, primary malnutrition due to lack of food is the most common cause. Malnutrition in a developed country such as Canada may be due to inadequate intake of nutrients, malabsorption and/or the hypercatabolism accompanying a critical illness. Protein-energy malnutrition is increasingly recognized in eating disorders such as anorexia nervosa.

12.2. Mechanism

More common reasons for malnutrition include the following.
- o Lack of food intake due to anorexia, depression or symptoms exacerbated by food intake (dysphagia, odynophagia, nausea, vomiting or abdominal pain)
- o Maldigestion. Examples include pancreatic disease and bile salt deficiency due to cholestatic hepatobiliary disease or ileal disease
- o Malabsorption. For example, mucosal disease of the small intestine or loss of intestinal surface area due to resection
- o Excessive loss of nutrients. For example, protein-losing enteropathy seen in many intestinal disorders
- o Medications. For example, cholestyramine used for bile salt induced diarrhea can worsen steatorrhea in the case of an extensive ileal resection
- o Alcoholism. Alcoholics rarely consume a well-balanced diet. They depend heavily on "empty" calories from alcohol. Protein and vitamin deficiencies, particularly of the B-complex group, are extremely common. Alcohol is a toxic agent that even in the presence of adequate nutritional intake can produce damage to the pancreas, liver and small bowel mucosa, aggravating malnutrition

12.3. Signs of Malnutrition
- o Weight loss
- o Muscle wasting. Particularly evident in the temporal area and dorsum of the hand between the thumb and index finger. It suggests protein-calorie deficiency

- o Signs of fat soluble vitamin (ADEK) deficiency. Decreased visual acuity, low bone mass, and easy bruising
- o Cheilitis. Fissures at corners of mouth due to riboflavin (B2), iron deficiency.
- o Glossitis. Due to B12, folate or iron deficiency
- o Hepatomegaly. Fatty liver is a common finding in protein malnutrition or alcoholism.
- o Peripheral neuropathy. Decreased position sense, decreased vibration sense or ataxia may result from B12 deficiency
- o Anemia. Can be due to iron, folate or B12 deficiency. Can be due to anemia of chronic disease
- o Peripheral edema (Hypoalbuminemia)

13. Acute Abdominal Pain / *J.M. Watters and N. Saloojee*

13.1. Description

Acute abdominal pain refers to pain that has been present for a short period of time, generally less than 24 hours. The term *acute abdomen* is best used to describe abdominal pain severe enough to suggest a serious intraabdominal condition. Although not entirely accurate, acute abdomen is sometimes used synonymously with peritonitis (peritoneal inflammation). Since some patients with an acute abdomen require resuscitation and early surgical treatment, it is important to assess the patient and establish a plan of management as soon as possible. The initial goal if the patient has an acute abdomen is not necessarily to make a definitive diagnosis, but rather to identify if the patient requires prompt surgical intervention.

13.2. Mechanism

Acute abdominal pain may be referred to the abdominal wall from intraabdominal organs (visceral pain) or may involve direct stimulation of the somatic nerves in the abdominal wall (somatic pain). Peritonitis results in somatic pain.

Visceral pain arises from such things as tension in the bowel wall (e.g., distension or vigorous contraction), mesenteric traction, or irritation of the mucosa or serosa of the bowel (e.g., chemical irritation, bacterial contamination, ischemia). Foregut pain is typically epigastric in location, midgut pain is central, and hindgut pain is felt in the lower abdomen. Organs that are bilateral give rise to visceral pain that is predominantly felt on one or the other side of the body.

Somatic pain is more precise in location than visceral pain. That is the main difference between the two. Somatic pain corresponds more directly to the anatomic site of the underlying pathology. Somatic pain occurs with stimulation of pain receptors in the peritoneum and abdominal wall.

Occasionally, pain is referred to the abdomen from extra-abdominal sites (e.g. lower lobe pneumonia). Unusually, acute abdominal pain is a feature of systemic disease (e.g. diabetic ketoacidosis).

13.3. History

The history should focus on the chronology, location, intensity and character of the pain. Aggravating and relieving factors should be sought. As always, inquire about associated symptoms, past medical and surgical history, medications, family and social history (including smoking, alcohol and substance abuse).

Severe pain of sudden onset may suggest a catastrophic event (e.g. perforation of an ulcer, intestinal ischemia, or rupture of an aortic aneurysm). Pain that occurs episodically is sometimes referred to as "colic". Colicky pain corresponds to peristaltic waves. It eases or

disappears between waves. One example is the intermittent, mid-abdominal pain of uncomplicated small bowel obstruction. Another is the intermittent flank pain radiating anteriorly to the groin that accompanying ureteric obstruction from a renal stone. Biliary "colic" is a misnomer, in that biliary pain is typically steady. It is usually felt in the epigastrium or right upper quadrant.

As mentioned visceral pain is poorly localized as compared to somatic pain. Nevertheless, the initial location of pain can provide a clue as to the origin. Also, radiation of pain may provide important clues to diagnosis. Irritation of the diaphragm, from peritonitis, for example, may cause shoulder tip pain. Biliary tract pain may radiate to the right scapular region. Pain arising from retroperitoneal structures may be perceived in the back (e.g. pancreatitis, leaking abdominal aortic aneurysm).

The character and subsequent evolution of acute abdominal pain may give a clue as to the site and nature of the underlying pathology. For example, pain with movement (e.g. riding in a car or walking) suggests the presence of peritonitis.

13.4. Associated Symptoms

Anorexia, nausea and vomiting are more common in diseases of the gastrointestinal tract but are not specific to a particular disorder. Abdominal distention and obstipation may suggest intestinal obstruction. Bloody diarrhea may arise from severely inflamed, ulcerated or infarcted bowel. Jaundice points to a hepatobiliary problem. In women, an accurate menstrual history is important. Urinary symptoms may suggest a genitourinary diagnosis (e.g. pyelonephritis, renal stones).

13.5 Physical Examination

In some patients with acute and severe abdominal pain, analgesics are delayed until after the physical exam. This generally applies to a subset of such patients presenting for evaluation in the emergency department. Analgesia may impair the sensitivity of physical examination when signs are subtle. Medication should be given promptly once the assessment has been completed. It should be given if the physical exam will be unavoidably delayed.

The physical exam begins with an evaluation of blood pressure, pulse and respiratory rate. Abdominal pathology may lead to systemic effects such as hypotension, tachycardia, or tachypnea. A careful physical examination will also identify pertinent extra-abdominal findings such as jaundice or lymphadenopathy.

Examination of the abdomen is performed with the patient supine. The steps are inspection, auscultation, palpation and percussion. Inspection of the abdomen should note any distention, mass, hernia, or scar. Of note is that the patient with peritonitis typically lies immobile. This is because any movement increases peritoneal irritation and pain.

Unlike examination of other systems, auscultation is often performed before palpation. Palpation can stimulate intestinal peristalsis and alter the result of auscultation. Auscultation may reveal a range of bowel sounds. A silent abdomen indicates an ileus or lack of intestinal peristalsis. Causes of ileus include the postoperative state, medications such as narcotics, or peritonitis. Hyperactive bowel sounds may be heard when a bowel obstruction is present. Bruits are sounds created by turbulent flow through a stenotic artery. When present, they suggest vascular disease.

Gentleness is the key to abdominal palpation. Palpation detects and localizes tenderness, muscle guarding, rigidity and masses. Palpation should begin in an area away from where pain is experienced, progressing to the area of pain last. Involuntary guarding and rebound tenderness are signs of peritonitis. Guarding refers to contraction of abdominal wall muscles when the

abdomen is palpated. Guarding is only important if muscle contraction is involuntary. Involuntary guarding occurs as a protective mechanism when peritoneal inflammation (peritonitis) is present. Voluntary guarding occurs when a patient tenses abdominal wall muscles in response to that abdominal wall pressure. It is a meaningless finding that is commonly seen. Guarding may be localized (e.g. uncomplicated appendicitis) or generalized throughout the abdomen (e.g. perforated appendicitis with diffuse contamination of the peritoneal cavity). In some instances of peritonitis, the muscles are in a state of continuous contraction. They are rigid or "board-like", even without palpation. In subtle situations, peritonitis is suggested by the triggering of pain in the area of suspected pathology (e.g., appendicitis) through palpation elsewhere on the abdominal wall, by having the patient cough or by gently shaking the pelvis.

Gentle percussion is also a very useful way to assess peritoneal irritation, as well as to assess the nature of abdominal distention. Rebound tenderness, another sign of peritonitis, is elicited by deeply palpating the area of concern and then suddenly releasing the abdominal wall. Severe pain felt on release of the abdominal wall is rebound tenderness. This manoeuvre can be very distressing to the patient with peritonitis, so it is often not done. Rectal and pelvic examinations should be carried out and recorded by at least one examiner. The sites for inguinal and femoral hernias should be specifically examined. Femoral pulses should be palpated.

13.6. Differential Diagnosis

The list of causes of abdominal pain is long. Table 5 provides a list of common or important conditions to consider. The list is not meant to be complete. Intra-abdominal conditions requiring surgery (open or laparoscopic) are the most common causes of an acute abdomen. Some conditions require immediate surgery (e.g. ruptured abdominal aneurysm). They must always be included in the differential diagnosis, therefore, and confirmed or excluded promptly. In other instances, the specific diagnosis and the need for surgery may take some time to establish. The likelihood of specific diagnoses varies to an extent with the age of the patient. Clinical presentations are more likely to be atypical in the elderly and in patients with coexisting conditions (such as diabetes or stroke). Particular care must be taken to not overlook an important intra-abdominal process in such patients.

One must always consider in the differential diagnosis: (1) intra-abdominal conditions for which surgery is not indicated (e.g. acute pancreatitis, (2) extra-abdominal (e.g. pneumonia) or systemic conditions (e.g. diabetic ketoacidosis) that can be accompanied by acute abdominal pain.

Table 5. Differential Diagnosis of Acute Abdominal Pain

o Peptic Ulcer Disease	o Bowel obstruction
o Mesenteric ischemia/infarction	o Diverticulitis
o Gastroenteritis	o Ruptured Abdominal Aortic Aneurysm
o Cholecystitis	o Incarcerated hernia
o Pancreatitis	o Hepatitis
o Appendicitis	o Pyelonephritis / Cystitis
o Functional Conditions (eg. irritable bowel syndrome, non ulcer dyspepsia)	o Gynaecologic conditions (ex. pelvic inflammatory disease, ruptured ectopic pregnancy)
o Inflammatory Bowel Disease	o Extra abdominal and Systemic Causes

13.7. Investigations

In many instances, a careful history and physical examination provide the clinical diagnosis. Complete blood count (CBC), serum amylase or lipase, electrolytes, creatinine, liver enzymes, glucose and urinalysis are routine. Other blood work is obtained as indicated. Pregnancy testing should be done when appropriate. Chest and plain abdominal x-rays are obtained routinely unless the diagnosis is clear (e.g. appendicitis). The presence of free peritoneal air indicates a perforated viscus. Abdominal x-rays can also provide information about the pattern of bowel gas (e.g. intestinal obstruction), edema and pneumatosis of the bowel wall, retroperitoneal structures (e.g. pancreatic calcification), and bony structures (e.g. fractures, bone metastases).

More sophisticated diagnostic imaging is often valuable. Ultrasound is very useful in the diagnosis of biliary tract disease (gallstones), abdominal aortic aneurysm, gynecologic disease and is often used in suspected appendicitis. Increasingly, abdominal CT scanning is being used, often obviating the need for more invasive or uncomfortable studies.

Other imaging modalities that may be ordered depending on the case include intravenous pyelography to assess the genitourinary tract or mesenteric angiography. The choice of investigation should be discussed with a radiologist.

Endoscopy (gastroscopy or colonoscopy) may be indicated in some cases. Laparoscopy has an important diagnostic role, as well as allowing definitive surgical therapy (e.g. appendectomy, omental patch of a perforated duodenal ulcer).

13.8. Approach to Management

A reasonably specific diagnosis or focused differential can usually be established early on. This is the basis for determining further management. In some instances (e.g. possible appendicitis), careful observation with repeated examination and selected imaging studies (e.g., ultrasound) allow a diagnosis to be reached. In some individuals, acute abdominal pain of mild to moderate severity resolves without a confirmed diagnosis. In patients with more serious conditions, intravenous fluid administration, other supportive measures and monitoring must be instituted following rapid initial assessment, even before a specific diagnosis can be made. In such individuals, diagnostic and therapeutic manoeuvres must proceed in a coordinated and efficient manner. Occasionally, patients with an acute abdomen, typically those who are unstable despite resuscitation or who have obvious generalized peritonitis, require urgent CT scan or ultrasound of the abdomen, or even laparotomy without a definitive preoperative diagnosis.

14. Chronic Abdominal Pain / *W.G. Thompson and N. Saloojee*
14.1. Description

As discussed below, there is a wide differential to chronic abdominal pain. In many cases however, no objective abnormality can be found. Such patients are said to have functional abdominal pain. Ten percent of children suffer recurrent abdominal pain and approximately 20% of adults have abdominal pain at least six times per year unrelated to menstruation. Functional abdominal pain syndrome is formally described as pain present continuously or near continuously for 6 months or more in which there is no relationship of the pain to eating, defecation, menses and in which no organic pathology can be found. Patients not strictly meeting this duration of pain may still be said to have functional abdominal pain.

14.2. Mechanisms and Causes

Functional abdominal pain is regarded is as being related to dysfunction of the brain-gut axis: pain is perceived in the abdominal region in the absence of pathology. The central nervous system and psychosocial stressors combine to lead to a heightened experience of pain.

Of course, chronic abdominal pain may be caused by many organic diseases. The pain of peptic ulcer disease may be food related and may improve with antacid. Most ulcers are related to Non Steroidal Anti inflammatory Drugs (NSAID) or *H. pylori* infection.

Intermittent obstruction of the cystic duct by a gallstone is known as biliary colic. Characteristically, patients experience significant episodic right upper quadrant (RUQ) and sometimes epigastric pain after meals. The pain may last hours in duration. However it subsides spontaneously and the patient is systemically well. Cholecystitis refers to a more long lasting, continuous pain in the same area due to impaction of a stone in the cystic duct. Subsequent dilation and inflammation of the gallbladder occurs. Such patients may have fever or be systemically unwell. Obstruction of the common bile duct with a stone (choledocholithiasis) results in pain and jaundice. The presence of fever in such a patient indicates infection due to stasis of material in the biliary tree (cholangitis).

Other causes of chronic or recurrent abdominal pain include chronic pancreatitis, intra abdominal neoplasms, inflammatory bowel disease, mesenteric ischemia, partial bowel obstruction, adhesions, renal colic and gynaecologic disorders.

As mentioned, functional abdominal pain is unrelated to eating, defecation or menses. Irritable bowel syndrome, is an almost identical disorder but is distinguished by disordered defecation. Functional abdominal pain may be due to a normal perception of abnormal gut motility or an abnormal perception of normal gut motility. It may not be due to the gut at all in that patients frequently have accompanying psychosocial difficulties.

14.3. Important Historical Points and Physical Examination Features

When chronic abdominal pain relates to a bodily function (defecation, eating, micturition or menstruation) investigation should focus upon the involved system.

Functional pain is more frequent in those who have had recent conflicts, have experienced a death in the family, or have become overly concerned with fatal illness. There may be a history of traumatic life events. Depression and anxiety are frequent. Patients with functional abdominal pain do not have alarm symptoms such as fever, weight loss, or rectal bleeding. Physical examination and lab tests are normal.

14.4. Diagnosis and Management

Diagnostic testing for chronic abdominal pain is similar to that for acute abdominal pain. Investigation involves a combination of bloodwork, urinalysis, diagnostic imaging and endoscopic testing. Management of organic causes of the chronic abdominal pain is directed at the underlying disease process.

For patients with functional abdominal pain, the physician's responsibility is to reassure the patient that no serious disease exists. A strong patient-physician relationship is needed. Where such a relationship does not exist, the patient may consult many doctors without satisfaction. The focus is to help the patient manage the pain, rather than cure it. It is important to investigate to a degree to reassure both patient and physician that the diagnosis is correct. However, it is also important not to continually repeat investigations in the belief something is being missed. Drugs, especially narcotics, should be used with restraint. Some individuals

benefit from low-dose antidepressants, as in other chronic pain syndromes. These patients test our skill in the art rather than the science of medicine.

15. Jaundice / *L.J. Scully and N. Saloojee*
15.1. Description

A state characterized by increased serum bilirubin levels (hyperbilirubinemia) and a yellow appearance due to deposition of bile pigment in the skin and mucus membranes.

15.2. Mechanism

Bilirubin is a waste product of hemoglobin metabolism. Interruption of the breakdown pathway at any of a number of steps, or a marked increase in load due to red blood cell destruction, results in an increase in serum bilirubin and if high enough, clinical jaundice. Under normal circumstances, senescent red blood cells are taken up and destroyed in the reticuloendothelial system. Through a number of steps the heme molecule of hemoglobin is converted to bilirubin which is, tightly bound to albumin, and transported in the plasma to the liver cells. Hepatocytes take up bilirubin, conjugate it to glucuronide and excrete the bilirubin diglucuronide in bile into the duodenum. In the bowel, bacteria break down bilirubin to urobilinogen, 80% of which is excreted in the feces, contributing to the normal stool colour. The remaining 20% of urobilinogen is reabsorbed and excreted in bile and urine (enterohepatic circulation of urobilinogen).

Functional defects in bilirubin metabolism or anatomic obstruction to excretion into the biliary system will result in an increase in serum bilirubin and jaundice. A large increase in the breakdown products of hemoglobin alone (e.g. hemolytic anemia) will cause an increase in serum unconjugated bilirubin. If the problem lies after the uptake and conjugation step, the increase is in serum conjugated bilirubin. In adults, aside from hemolysis or the common benign unconjugated hyperbilirubinemia of Gilbert's syndrome, most patients with jaundice have a conjugated hyperbilirubinemia. Causes of jaundice are usually classified as: (1) hemolysis; (2) genetic defects in bilirubin handling; (3) hepatocellular disease; and (4) obstruction or cholestasis.

15.3. Clinical Presentation

Clinical jaundice is detected when the serum bilirubin level reaches 2–4 mg/dL (40–80 μmol/L). Jaundice is usually preceded by a few days of pale stools (as excretion of bilirubin into the intestine is decreased) and dark urine (due to increased glomerular filtration of conjugated bilirubin). Jaundice is usually first detected in the sclera, although the bilirubin is actually deposited in the overlying conjunctival membranes. Yellow skin without scleral icterus should suggest carotenemia (excess intake of foods high in carotene) or the ingestion of such drugs as quinacrine.

Patients with jaundice due to a hepatocellular cause (e.g. viral hepatitis) often have nausea, anorexia, hepatomegaly and right upper quadrant discomfort. Patients with jaundice due to a cholestasis often experience pruritis, presumably from deposition of bile salts in the skin. Physical exam may reveal an abdominal mass such as a dilated gallbladder. Other historical points to ask include inquiring about viral hepatitis risk factors (e.g. IV drug use, prior transfusions), history of alcohol abuse, medications, and family history of liver disease.

The end stage of liver disease of any cause is cirrhosis of the liver. Such patients have a small, shrunken and nodular liver. Signs or so-called stigmata of chronic liver disease may be found. These include spider nevi, gynecomastia, palmar erythema, Dupuytrens contracture, signs

of portal hypertension (ascites, splenomegaly, dilated periumbilical veins) and asterixis (flapping of the outstretched hands, a sign of hepatic encephalopathy).

15.4. Approach to Diagnosis

Initially, the evaluation of jaundice is to determine whether it is primarily due to conjugated or unconjugated hyperbilirubinemia (Figure 2). Serum bilirubin can be fractionated from total bilirubin into conjugated and unconjugated. The presence of bile in the urine determined by a test strip at the bedside confirms that the bilirubin rise is predominantly in the conjugated form. If the bilirubin is primarily unconjugated, hemolysis or genetic defects are implicated. A blood smear showing schistocytes or fragmented red calls confirms hemolysis. In adults, Gilberts syndrome is an inherited genetic disorder of impaired bilirubin conjugation. Particularly at times of physiologic stress, a mild unconjugated hyperbilirubinemia may occur. The disorder is innocuous and follows a benign natural history.

If the hyperbilirubinemia is conjugated, liver enzyme tests (AST, ALT, GGT and alkaline phosphatase) will help determine if the jaundice is primarily due to hepatocellular damage (high AST and ALT) or obstruction/cholestasis (high GGT and alkaline phosphatase). Transaminases (AST/ALT) are released by damaged hepatocytes. Also check the patients INR and albumin concentration, as these are markers of synthetic function of the liver and reflect a more chronic underlying disease process.

Cholestatic jaundice requires an ultrasound as the best, first test. Dilation of intra- and/or extrahepatic bile ducts indicates an anatomic problem. In this case, the cholestasis is caused by an extrahepatic problem (e.g. pancreatic neoplasm compressing common bile duct or stones in the common bile duct). Lack of biliary dilation indicates intrahepatic cholestasis (e.g. medication adverse effect).

Further tests such as viral serology, markers for other liver diseases, further liver imaging, endoscopic retrograde cholangiopancreatography (ERCP), MRI of the biliary area (MRCP), CT scan of the abdomen, and liver biopsy are ordered as needed.
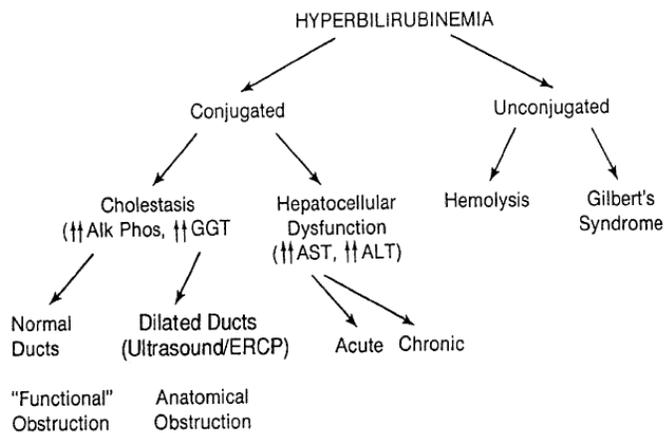
Figure 2. Approach to hyperbilirubinemia.

15.5. Management

Management of the specific disorders causing jaundice is contained in the chapters on the hepatobiliary and pancreatic systems. In general, hepatotoxins (e.g. alcohol, medication) should be withdrawn, biliary obstruction should be relieved if present, and therapy for the underlying disorder instituted where possible.

16. Ascites in Chronic Liver Disease / *L.J. Scully and N.Saloojee*

16.1. Definition

Ascites is the accumulation of free fluid in the peritoneal cavity.

16.2. Mechanisms

With significant liver disease (cirrhosis), ascites is a result of activation of the renin-angiotensin-aldosterone system and portal hypertension. Renin-angiotension-aldosterone activation leads to sodium and water retention. Increased portal pressure leads to transudation of fluid from the capillaries in the portal system to the peritoneal cavity. Ascites may also occur in patients without liver disease. Intra-abdominal malignancy or chronic peritoneal infection (e.g. tuberculosis) can lead to ascites as a result of protein rich fluid being actively secreted.

16.3. Signs and Symptoms

Ascites most commonly presents with increasing abdominal girth. There is often an uncomfortable feeling of distention. Sometimes, there is nausea and anorexia. Diaphragmatic elevation or a pleural effusion (ascites fluid tracking into pleural space) can lead to shortness of breath. Ankle edema may accompany ascites. Clinical examination reveals a distended abdomen and bulging flanks on inspection. "Shifting dullness" or a "fluid thrill" may be elicited. Smaller amounts of fluid may be detected on ultrasound when clinical signs are absent. One should look for other signs of portal hypertension, such as dilated abdominal wall veins or splenomegaly.

16.4. Differential Diagnosis

Newly developed ascites must have a diagnostic aspiration (paracentesis) to determine the albumin level, cell count and cytology. The fluid should be clear and straw coloured. If the fluid is bloody, chronic infection (e.g. tuberculosis) or malignancy should be sought. Determining the etiology of ascites hinges on the serum ascites albumin gradient (SAAG). The gradient is calculated by subtracting the ascites albumin from the serum albumin. If the gradient is high (>11 g/L), then the ascites is due to portal hypertension. If the gradient is low (>11 g/L), then the ascites is not from portal hypertension. The likeliest cause of low gradient ascites is malignancy. A low gradient results from ascites that is high in protein, so that the ascites albumin level is close to that of the serum.

Ascitic fluid may become infected, in which case the white blood cell count will be elevated (>250 neutrophils/uL) in the fluid. Bacterial infection of ascites fluid can be due to a perforation in the GI tract (e.g. perforated appendix) or it can be a spontaneous occurrence (spontaneous bacterial peritonitis).

16.5. Approach to Management

Management of ascites begins with salt restriction. Most cases also require addition of a diuretic such as spironolactone and/or furosemide. If ascitic fluid reaccumulates despite these measures, aspiration of large quantities of ascites fluid or large volume paracentesis may be

necessary. Six to eight litres can be safely removed at a time. If ascites remains uncontrolled, options include repeated large volume paracentesis, transjugular intrahepatic portosystemic stent shunt (TIPS) or liver transplant.

This topic is covered extensively in the chapter "Ascites".

17. Gastrointestinal Bleeding / *A. Rostom, C. Dubé and N.Saloojee*
17.1. Description

Gastrointestinal (GI) bleeding may be referred to as upper, lower, obscure or occult. Upper GI bleeding commonly presents with hematemesis (vomiting of red blood), coffee-ground emesis and/or melena (black, tarry stools). The black colour of melena is the result of degradation of blood by intestinal bacteria. In comparison, hematochezia (bright red or maroon coloured blood per rectum) is usually a sign of lower GI bleeding. It is important to note that a very brisk upper GI bleed can lead to hematochezia as blood passes rapidly through the gut and is not degraded. Upper GI bleeding occurs proximal to the ligament of Treitz. Small bowel bleeding occurs from the ligament of Treitz to the distal ileum. Lower GI bleeding occurs from the terminal ileum and colon.

Occult bleeding is bleeding that is not apparent to the patient. The quantity of bleeding is small, so that the colour of stools is not altered. Patients may present with a positive fecal occult blood test (FOBT) result and/or iron-deficiency anemia (IDA). Chronic loss of small amounts of blood can eventually lead to significant IDA. Obscure bleeding is defined as bleeding of unknown origin that persists or recurs after negative initial endoscopies (colonoscopy and upper endoscopy). Most commonly, the source of obscure bleeding is the small bowel. Obscure bleeding may be overt (i.e., hematemesis, melena or hematochezia), or may be occult such as persistent IDA. The important causes of upper and lower GI bleeding are presented in Tables 3 and 4 respectively.

Table 6. Causes of Upper GI Bleeding

Common	**Less Common**
o Peptic Ulcer Disease : Gastric Ulcer, Duodenal Ulcer	o Esophagitis
o Esophageal Varices	o Portal Hypertensive Gastropathy
o Mallory-Weiss Tear	o Vascular : angiodysplasia, gastric antral vascular ectasia (GAVE; "watermelon" stomach), Dieulafoy lesion)
o Neoplasm : Esophageal cancer, Gastric Cancer, Lymphoma	o Aortoenteric Fistula
	o Hemobilia
	o Crohn disease

Table 7. Causes of Lower GI Bleeding

Common	**Less Common**
o Diverticular bleed	o Radiation Proctitis
o Angiodysplasia	o Post-polypectomy bleeding
o Colon Cancer	
o Ischemic Colitis	
o Inflammatory Bowel Disease	

17.2. Approach to Diagnosis and Management

The initial evaluation of the patient with acute GI bleeding involves assessment of the "ABCs" (Airway, Breathing, and Circulation). Patients with upper GI bleeding are at risk of airway compromise from aspiration of vomited blood. Another risk factor for some patients is a reduced level of consciousness due to shock or hepatic encephalopathy. Some patients may require supplemental oxygen or even intubation for airway protection and/or assisted breathing. During the assessment of the hemodynamic status, IV access is crucial. In a significant GI bleed, two large bore peripheral IVs (18 gauge or greater) are placed for fluid and blood product restoration. At this stage, blood should be drawn for typing and cross-matching. Bloodwork should include CBC, INR, electrolytes, urea, creatinine, as well as albumin and liver enzymes.

It is important to remember that, hemoglobin (Hb) and hematocrit (Hct) may not be low at presentation. These measures reflect the red blood cell concentration. Over the ensuing 36–48 hours, most of the volume deficit will be repaired by the movement of fluid from the extravascular into the intravascular space. Only at these later times will the Hb and Hct reflect the true degree of blood loss. Furthermore, if a patient presents with an acute GI bleed and the initial Hb is low, one should expect the Hb to continue to decline and so transfusion should be considered. Some patients, in particular those with GI malignancies, may have had chronic occult bleeding prior to their acute presentation. The result is hypochromia and microcytosis from iron deficiency. Coagulopathy, due to medications (e.g. warfarin) or liver dysfunction, should be corrected. An elevated blood urea nitrogen (BUN) value in the presence of a normal creatinine may be a sign of upper GI bleeding. The elevated BUN is due to blood being absorbed from the proximal small bowel.

Pharmacotherapy for GI bleeding includes intravenous proton pump inhibitors in cases of suspected bleeding from peptic ulcer disease and intravenous administration of somatostatin analogs (octreotide) in suspected cases of esophageal variceal bleeding. Because of the seriousness of upper GI bleeding, and the not-uncommon delay in obtaining in endoscopy for purposes of diagnosis and endoscopic hemostatic therapy, pharmacotherpy is often given on initial presentation, before the cause of bleeding has been definitively determined.

In acute GI bleeding, symptoms associated with blood loss include weakness, diaphoresis, pre-syncope, and syncope. Patients with a chronic, slow bleed may present with iron deficiency anemia. Signs and symptoms include pallor, fatigue, and dyspnea. In a predisposed individual, anemia can lead to congestive heart failure or angina. In all cases of GI bleeding, information should be gathered about medication use, in particular the intake of NSAIDs, Aspirin (ASA) or anticoagulants. Other important data includes a prior history of peptic ulcer disease, history of abdominal surgery (e.g. vascular grafts raise the suspicion of aorto-enteric fistulas), and a history of chronic liver disease or alcohol abuse. Look for signs of chronic liver disease on physical examination. The hemodynamic status should be interpreted in light of the patient's abilities to compensate for hypovolemia. In a young and fit adult, the presence of a resting or orthostatic tachycardia should be interpreted as a sign of significant volume loss, while the loss of an equivalent blood volume in an elderly or debilitated subject would more likely be manifested by hypotension or shock.

Once supportive measures have been undertaken, the patient should be assessed with a view towards identifying the source of bleeding (ie. upper or lower). Bright red emesis is suggestive of bleeding from esophageal varices or of a brisk upper GI source. In a duodenal bleed, blood may or may not reflux into the stomach. Therefore, the absence of hematemesis, coffee ground emesis or a bloody aspirate from nasogastric suction does not rule out an upper GI

bleed. The pigmentation of the stool will depend on the length of time in transit along the bowel. In an upper GI bleed, transit time is usually longer than a lower bleed. Therefore, an upper GI or proximal small bowel bleed usually leads to melena. Conversely, a lower GI bleed generally leads to hematochezia. In determining the likely source of bleeding, the clinician needs to interpret the patient's manifestations of bleeding in conjunction with the hemodynamic status. Blood originating from the left colon typically is bright red. However, hematochezia associated with hemodynamic instability raises the suspicion of a brisk upper GI bleed. Similarly, while the passage of melena is most commonly associated with an upper GI source, dark burgundy or black stools can sometimes be encountered in proximal colonic bleeds. In the absence of spontaneous passage of stools, a digital rectal examination to determine the stool color will be most informative.

Under certain circumstances it may be difficult to determine if the GI bleed, particularly if it is significant, is of upper or lower origin. It is then safest to proceed on the assumption of an upper GI bleed, and to arrange for early upper endoscopy. Many causes of upper GI bleeding are amenable to endoscopic therapy. If the bleed is due to a peptic ulcer, upper endoscopy allows stratification of rebleed risk based on the appearance of the ulcer. In a suspected upper GI bleed, the timing of upper endoscopy varies. Early upper endoscopy is done if there are signs of a brisk bleed, a variceal bleed is suspected, the patient is older or has numerous comorbidities.

Most lower GI bleeds stop spontaneously, so the treatment is mainly supportive. If a lower GI bleed does not stop, angiography should be pursued to localize the source of bleeding and possibly embolize the source. If these measures fail to stop a lower GI bleed, surgery may become necessary. Colonoscopy has little utility in an active lower GI bleed since blood obscures visualization. The role of colonoscopy in lower GI bleeding is mainly diagnostic, once bleeding has slowed and bowel cleansing can be achieved.

In the case of a GI bleed where upper endoscopy and colonoscopy are negative, small bowel investigations may become necessary. Radiologic options include a small bowel follow through or CT enterography (protocol to look at small bowel). Wireless capsule endoscopy involves ingestion of a pill sized camera to take pictures of the small bowel. Enteroscopy involves a long scope inserted from the mouth to examine the proximal small bowel. Balloon enteroscopy is a newer endoscopic technique in which total endoscopic examination of the small bowel is possible.

18. Abdominal Mass / *S. Grégoire and N. Saloojee*
18.1. Description

When an abdominal mass is discovered on physical examination, one must define its nature. Using a systematic approach often permits the identification of the mass before the use of sophisticated tests.

18.2. Important Points in History and Physical Examination

Important clues in the history and general physical examination may help to identify the enlarged viscus. For example, in a young patient presenting with diarrhea, weight loss and abdominal pain, finding a right lower quadrant mass would suggest inflammatory bowel disease. However, an abdominal mass may be discovered during physical examination of an asymptomatic individual. Certain observations made during the abdominal examination may be helpful (See also Section 20).

18.2.1. Inspection

Where is the mass located? A practical approach is to divide the abdomen into four quadrants (See Section 20.1). Starting from the principle that an abdominal mass originates from an organ, surface anatomy may suggest which one is enlarged. A mass seen in the left lower quadrant, for example, could be of colonic or ovarian origin but, unless there is situs inversus, one would not consider an appendiceal abscess. Does the mass move with respiration? In the upper abdomen a mobile intraabdominal mass will move downward with inspiration, while a more fixed organ (e.g. aorta, pancreas) or an abdominal wall mass (e.g. hematoma of the rectus muscle) will not.

18.2.2. Auscultation

Careful auscultation for bowel sounds, bruit or rub over an abdominal mass is part of the systematic approach.

18.2.3. Defining the Contour and Surface of the Mass

This is achieved by inspection, percussion and palpation. Is the organ air filled (e.g. stomach) or fluid-filled? Is it a well-defined mass (e.g. liver, spleen) or are its borders difficult to define (e.g. matted loops of small bowel)? Is the surface regular? An enlarged liver due to fatty infiltration may have a smooth surface. What is the consistency of the mass? Firm, hard or soft? Is it pulsatile to suggest an aortic aneurysm? In the absence of ascites, ballottement of an organ situated in either upper quadrant more likely identifies an enlarged kidney (more posterior structure) than hepatomegaly or splenomegaly.

18.3. Differential Diagnosis

The following suggests an approach to the differential diagnosis of an abdominal mass located in each quadrant:

18.3.1. Right Upper Quadrant

This location suggests liver, right kidney, gallbladder and, less commonly, a colon or gastroduodenal mass. A pancreatic mass is rarely palpable.

Liver: As a subdiaphragmatic organ, the liver moves downward with inspiration. This anterior organ has an easily palpable lower border, which permits assessment of its consistency. An enlarged left lobe can usually be felt in the epigastric area.

Right kidney: The kidney may protrude anteriorly when enlarged and be difficult to differentiate from a Riedel's lobe of the liver. It may be balloted.

Gallbladder: This oval-shaped organ moves downward with inspiration and is usually smooth and regular.

Colon: Colon masses are deep and ill-defined, and do not move with respiration. High-pitched bowel sounds suggest obstruction.

18.3.2. Left Upper Quadrant

Location in the left upper quadrant suggests spleen or left kidney. Less commonly, a colonic (splenic flexure) or gastric mass can be felt. A pancreatic mass is rarely palpable.

Spleen: This anterior organ moves downward with inspiration. Since it has an oblique longitudinal axis, it extends toward the right lower quadrant when enlarged. It has a medial notch and the edge is sharp.

Left kidney: Its more posterior position and the presence of ballottement helps distinguish the left kidney from the spleen.

Colon, pancreas, stomach: It is practically impossible to differentiate masses in these organs by physical examination. The history helps but often one must resort to radiology or endoscopy.

18.3.3. Right Lower Quadrant

A mass in this area has its origin either in the lower GI tract (colon, distal small bowel, appendix) or in a pelvic structure (ovary, uterus, fallopian tube).

Lower GI tract: These deeper organs are usually ill-defined. Clinical context is important. Inflammatory bowel disease usually would be associated with pain on palpation but carcinoma of the cecum would be painless.

Pelvic organs: Bimanual palpation is the preferred method.

18.3.4. Left Lower Quadrant

As with a right lower quadrant mass, the differential diagnosis here is between lower GI (in this quadrant the sigmoid colon) and pelvic origin. Pelvic examination may help differentiate the two.

18.4. Approach to Diagnosis

To complete the assessment of an abdominal mass, one may choose among several different investigational tools. The use of specific tests depends on availability and on the organ studied. Generally, ultrasound is useful. This noninvasive, safe, cheap and widely available method identifies the mass and provides information on its origin and nature. Ultrasound may also be used to direct a biopsy. Other noninvasive modalities are CT scan and MRI. Hollow organs may be demonstrated radiographically through the use of contrast media (e.g., air contrast barium enema, upper GI series, intravenous pyelogram, endoscopic retrograde cholangiopancreatography [ERCP]). Sometimes, laparotomy or laparoscopy will be necessary to make the diagnosis.

19. Proctalgia Fugax / *W.G. Thompson and N. Saloojee*
19.1. Description

Proctalgia fugax is a sudden severe pain in the anus lasting several seconds or minutes and then disappearing completely.

19.2. Mechanism

The pathophysiology of proctalgia fugax is uncertain. Although some observations suggest a rectal motility disorder, the symptom appears more likely to result from spasm of the skeletal muscle of the pelvic floor (specifically, the puborectalis).

19.3. History and Physical Examination

Proctalgia fugax occurs in about 14% of adults and is somewhat more common in females than males. The pain may be excruciating, but since it is so short-lived patients seldom report it to their physician. In 90% of instances it lasts less than five minutes and in many cases less than a minute. About one third of patients suffer attacks following defecation. A small minority report attacks following sexual activity. There are no physical signs.

19.4. Differential Diagnosis

Perianal disease may cause pain but it usually accompanies, rather than follows, defecation. One should be particularly careful to exclude the presence of an anal fissure, which may be difficult to see on anal inspection. Pain originating from the coccyx may be accompanied by coccygeal tenderness both externally and from within the rectum. An acute attack of anal pain lasting several hours may indicate a thrombosed hemorrhoid.

19.5. Management

Beyond reassurance, there is no specific treatment.

20. Examination of the Abdomen / *R.F. Bursey, J.M. Fardy, D.G. MacIntosh and N. Saloojee*

Examination of the abdomen is an important component of the clinical assessment of anyone presenting with suspected disease of the gastrointestinal tract. As in all other parts of the examination, care must be taken to show respect and concern for the patient while ensuring an appropriate and thorough examination. While performing the examination it is useful to keep in mind the concepts of sensitivity and specificity. How confident can we be that a suspected physical finding is in fact present and has clinical significance? For example, how sensitive and specific is our bedside examination for hepatomegaly? What is the clinical significance of an epigastric bruit heard in a thin 20-year-old female versus a 55-year-old hypertensive, obese male? In the following sections we will describe an appropriate sequential examination of the abdomen and highlight some of the potential pitfalls of this process.

20.1. Inspection

Start from the usual position to the right side of the supine patient. The patient should not have a full bladder. Ensure that the abdomen is exposed from the costal margin to symphysis pubis. Positioning is important. The patient should keep his or her arms by the sides or folded across the chest. Ensure the patient does not have his or her legs crossed. When describing the location of an abnormality it is useful to divide the abdomen into four quadrants. Imagine a perpendicular line through the umbilicus from the xiphoid process to the symphysis pubis. A horizontal line through the umbilicus then allows the abdomen to be divided into 4 areas: the left upper, right upper, left lower and right lower quadrants (Figure 3). On occasion it may be helpful to divide the abdomen into 9 regions with the spaces marked by vertical lines through the left and right mid-clavicular lines and horizontal lines passing through the subcostal margins and anterior iliac crests (Figure 4).

The overall appearance of the abdomen can be described as scaphoid (markedly concave), protruberant, or obese. The location of any surgical scars noted. One should examine the skin for cutaneous lesions, vascular markings, dilated veins and striae. Note any pulsation that could indicate an aneurysm. Note the movement of the abdominal wall with respiration. Normally the abdominal wall will rise with inspiration. Occasionally organomegaly or a mass will be visible. It is helpful to look at the abdomen from the foot of the bed as well.
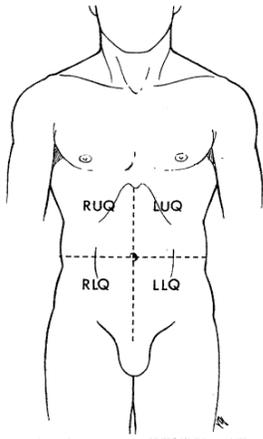
Figure 3. Division of the abdomen into four quadrants: the left upper quadrant, right upper quadrant, left lower quadrant and right lower quadrant.
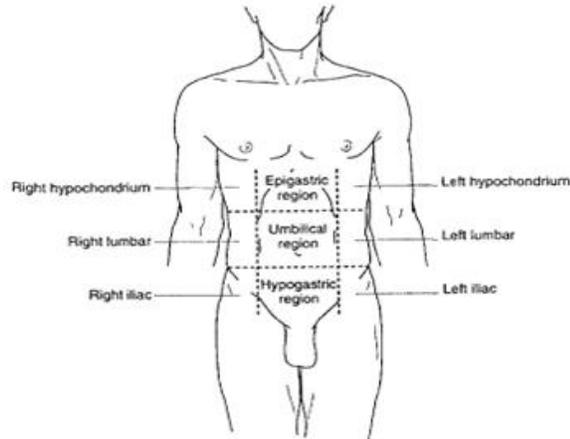
Figure 4. Division of the abdomen into nine regions.

20.2. Auscultation

It is useful to auscultate the abdomen for bowel sounds and bruits prior to palpation or percussion. Palpation or percussion will stimulate peristalsis and may mask vascular bruits. When listening for vascular bruits it is useful to keep in mind Figure 4. Bruits are vascular sounds created by turbulent flow and may indicate partial arterial occlusion. Arterial bruits are usually heard only during systole and best heard with the diaphragm of the stethoscope, as they are high pitched. Listen for the aorta in the epigastrium. Renal bruits may be heard midway between the xiphoid process and the umbilicus, 2 cm away from the midline. Listen for iliac bruits halfway between the umbilicus and the inguinal ligament. One should listen over the inguinal ligament for femoral bruits as well.

About 20% of normal persons will have a vascular bruit, so that the auscultation of an abdominal bruit has to be placed within the clinical context.

A venous hum is a rare sound, best heard overlying the portal vein. This is found an area approximated by an ellipse between the umbilicus and the midclavicular line where it crosses the right subcostal margin. A venous hum can occur in portal venous hypertension of any cause. There are, however, no studies to suggest this is a helpful finding in routine examination.

Friction rubs are a rare sound indicating inflammation of the peritoneal surface of an organ. They are grating in quality and vary with respiration. They may occur over a liver tumour. However, even with careful auscultation of patients with known liver tumours, fewer than 10% are found to have a rub.

20.2.1. Bowel Sounds

Bowel sounds should be listened for prior to palpation or percussion, but the yield of this examination is low. The diaphragm of the stethoscope should be placed on the abdomen. Listening in one spot, such as the right lower quadrant, is generally sufficient since bowel sounds are transmitted widely through the abdomen. Rushes of very high pitched bowel sounds

coinciding with crampy pain may indicate hyperperistalsis and acute small bowel obstruction. Complete absence of bowel sounds may indicate an ileus or peritonitis.

20.3. Palpation

Palpation of the abdomen should be done in an orderly sequence with the patient in the supine position. Light palpation should be done in all four quadrants, assessing for areas of potential tenderness. If the patient complains of pain, palpate that area last. With one hand, using the pads of the fingertips, palpate in a gentle, circular motion. If no areas of obvious tenderness are elicited, then deep palpation is performed. This is again done in all four quadrants, however use both hands. One hand is placed on the abdominal wall. The second hand is placed over top of the first. It is thought that using one hand for deep palpation may increase the risk of missing a mass. The accuracy of this has not been tested.

Involuntary guarding and rebound tenderness are signs of peritoneal inflammation (peritonitis). Guarding refers to contraction of abdominal wall muscles when the abdomen is palpated. Guarding is only important if muscle contraction is involuntary. Involuntary guarding occurs as a protective mechanism when peritonitis is present. Voluntary guarding occurs when a patient tenses abdominal wall muscles in response to that abdominal wall pressure. It is a meaningless finding that is commonly seen. Guarding may be localized (e.g uncomplicated appendicitis) or generalized throughout the abdomen (e.g. perforated appendicitis with diffuse contamination of the peritoneal cavity). In some instances of peritonitis, the muscles are in a state of continuous contraction. They are rigid or "board-like" even without palpation. In subtle situations, peritonitis is suggested by the triggering of pain in the area of suspected pathology (e.g., appendicitis) through palpation elsewhere on the abdominal wall, by having the patient cough or by gently shaking the pelvis.

Rebound tenderness, another sign of peritonitis, is elicited by deeply palpating the area of concern and then suddenly releasing the abdominal wall. Severe pain felt on release of the abdominal wall is rebound tenderness. This manoeuvre can be very distressing to the patient with peritonitis, so it is often not done. The sites for inguinal and femoral hernias should be specifically examined. Femoral pulses should be palpated.

The techniques of palpation of liver and spleen are discussed in Sections 20.5 and 20.6.

20.4. Percussion

Percussion of the abdomen will detect the presence of bowel gas. It is useful in defining organomegaly and the presence of free intra-abdominal fluid (ascites), as discussed below.

20.5. Examination of the Liver

First, inspect for a right upper quadrant mass. The examiner should look for stigmata of chronic liver disease (section 15.3). Next, palpate for the lower edge of the liver.

To palpate the liver edge, start in the right lower quadrant of the abdomen. The edge of an enlarged liver may be missed by starting too high in the abdomen. The patient is asked to breathe deeply and slowly, in order to bring the liver edge down to the examining fingertips of the right hand. The examiner moves the right hand in a cephalad direction about 2 cm with each expiration. If the edge is not felt, no further examination is required.

The liver, if palpable, is normally smooth and regular. Note any firmness, irregularity or nodularity to suggest an abnormal liver. Interobserver agreement about such characteristics is poor, even among experts. Note any tenderness. When the liver edge is palpable, trace the edge

working laterally to medially. If the liver edge is palpated, the liver span should be measured by percussion. Start by percussing in the right midclavicular line in an area of tympany. Percuss in a cephalad direction in the right midclavicular line until an area of dullness is encountered. This is the lower border of the liver. Percuss for the upper border starting in the right midclavicular line in the third intercostal space. Move down one interspace at a time until the percussion note changes from resonant to dull. To confirm the change of percussion note strike the third and fourth fingers laid in adjacent interspaces. The note on the top finger should be resonant and on the lower dull. This is the upper border of the liver. Measure the distance between the upper and lower percussion edges in the mid-clavicular line. Percussion typically underestimates the true vertical span on the liver.

The scratch test has been used to find the lower liver margin. The diaphragm of the stethoscope is placed at the right costal margin in the midclavicular line. A finger moves up the abdomen in the mid-clavicular line, scratching gently and with consistent pressure. When the liver edge is reached, there is a sudden increase in the scratching sound heard through the stethoscope. In one comparative study the scratch test was not felt to offer any advantage over the techniques of palpation and percussion.

What is the significance of a palpable liver edge? One review suggested that a palpable liver is not necessarily enlarged or diseased. When clinical examination is compared to nuclear medicine scanning, about one-half of palpable livers are not enlarged. The inability to feel a liver edge does not rule out hepatomegaly, but does reduce its likelihood. What is the normal percussion span? Only one study has been done to establish the normal span. Castell examined 116 healthy subjects using firm percussion. The mean span in the mid-clavicular line was 7 cm in women and 10.5 cm in men (8±2 cm in women and 11±2 cm in men is considered to be normal).

The following nomograms were developed to predict estimated liver dullness in a normal population using firm percussion technique. Male liver dullness equals (0.032 x weight in pounds) + (0.183 x height in inches) – 7.86. The female liver dullness equals (0.027 x weight in pounds) + (0.22 x height in inches) – 10.75. The 95% confidence intervals were ±2.64 cm. Therefore a 5 ft. 10 in., 175 lb. male would have an estimated liver span of 10.2 cm (range 7.6–12.8) and a 5 ft. 5 in., 130 lb. female would have an estimated liver span of 7.1 cm (4.5–9.7 cm) by this formula. These formulae are not used in day to day clinical practice.

Unlike the kidney in the left upper quadrant, the spleen moves downward and medially with inspiration, and does not have a notch.

20.6. Examination of the Spleen

The normal spleen is a curved, wedge-shaped organ located beneath the rib cage in the upper left quadrant. The spleen lies beneath the left tenth rib and normally weighs about 150 g. It is approximately 12 cm in length, 7 cm in width and 3 cm in thickness. The normal spleen usually cannot be palpated, but as it enlarges it descends below the rib cage and across the abdomen toward the right lower quadrant. An enlarged spleen may have a palpable notch along its medial edge. Examination of the spleen should begin with observation of the left upper quadrant for an obvious mass, though such a mass is quite uncommon.

The examiner should then proceed with percussion over the area of the spleen to look for evidence of dullness, implying splenic enlargement. The two most useful methods are percussion over Traube's space and Castell's sign. The surface markings for Traube's space are the left sixth rib, the left midaxillary line and the left costal margin. An enlarged spleen may cause

dullness over Traube's space. Percussion should be carried out at one or more levels of Traube's space from medial to lateral. This maneuver has a sensitivity and specificity between 60 and 70% for splenic enlargement. The sensitivity and specificity increases to approximately 80% in non-obese patients who are fasting.

Castell's method involves percussion in the lowest intercostal space in the left anterior axillary line. In normal individuals this area is resonant on percussion and remains resonant on inspiration. In patients with mild splenic enlargement this area will be resonant on percussion and become dull on maximal inspiration. This method has a sensitivity and specificity of approximately 80% for detection of splenic enlargement and is helpful for detection of a minimally enlarged spleen that may not be palpable.

Palpation of the spleen should begin in the right lower quadrant and proceed toward the left upper quadrant in order to follow the path of splenic enlargement. Palpation should initially be carried out in the supine position with a bimanual technique using the left hand to gently lift the lowermost portion of the left rib cage anteriorly. The fingertips of the right hand are used to palpate gently for the spleen tip on inspiration. The hand is moved from the right lower quadrant, advancing toward the left upper quadrant. If the spleen is not palpated in the supine position, the patient should be moved into the right lateral decubitus position and again with bimanual technique the spleen tip should be sought using the fingertips of the right hand on inspiration. This technique has a sensitivity of about 70% and specificity of 90% for splenic enlargement.

20.7. Examination for Suspected Ascites

The presence of ascites, free fluid within the abdominal cavity, is always due to an underlying pathological process (see section 16). Potential causes include cirrhosis, severe right-sided heart failure, primary intra-abdominal malignancy, peritoneal metastases, chronic infection such as tuberculosis, and lymphatic obstruction. It is easy to identify large-volume ascites clinically, but the sensitivity of the examination techniques falls with lower volumes of fluid. Ultrasound, which can detect as little as 100 mL of free fluid, is the gold standard against which the clinical diagnostic maneuvers are compared.

An approach involves inspection for bulging flanks, palpation for the presence or absence of fluid waves, and percussion to demonstrate shifting dullness. Bulging flanks are suggestive of ascites since fluid sinks with gravity, while gas filled bowel loops float to the top. Adipose tissue in the flanks may be occasionally mistaken for free fluid.

To demonstrate a fluid wave it is necessary to enlist the aid of the patient or another individual. With the patient in the supine position, the examiner places one palm on the patient's flank. The patient or an assistant places a hand on the mid-abdomen. This is to apply sufficient pressure to dampen any wave that may pass through adipose tissue in the anterior abdominal wall. The examiner then briskly taps the opposite flank. If fluid is present, a shock wave will be felt with the palpating hand. The sensitivity of this technique is approximately 50% but it has a specificity of greater than 80%.

To test for shifting dullness, percuss from resonance in the mid-abdomen to dullness in the flanks. The area of transition is then marked and the patient rolled to the opposite side. For example, if flank dullness is demonstrated on the left then the patient should be rolled onto the right side. One should allow approximately 30 seconds for the fluid to move between the mesentery and loops of bowel into the inferior portion of the abdomen. The previous area of dullness in the left flank should now be resonant. It does not matter which side one chooses to start with. In three separate studies shifting dullness had a sensitivity that ranged from 60–88%

and a specificity that ranged from 56–90%. In one study involving six gastroenterologists and 50 hospitalized alcoholic patients, the overall agreement was 75% for the presence or absence of ascites and reached 95% among senior physicians (i.e. experienced). The absence of a fluid wave, shifting dullness or peripheral edema is also useful in ruling out the presence of ascites.

21. Oral-Cutaneous Manifestations of GI Disease / *N. Saloojee*
21.1. Description
 A number of gastrointestinal disorders are associated with oral or cutaneous manifestations. Some of the more common of these are presented here.

21.2. Specific Disorders
1. Glossitis. Inflammation of the tongue which can occur in a number of conditions. Seen in nutritional deficiencies such as iron or B12 deficiency. The tongue is smooth and can be enlarged.
2. Oral thrush. Candidiasis involving the oropharynx. When seen in association with dysphagia, the patient likely has esophageal candidiasis.
3. Cutaneous manifestations of Inflammatory Bowel Disease (IBD). Aphthous ulcers may occur in the oral mucosa of patients with IBD. Generally these lesions follow the course of the disease. They are seen when the intestinal disease is active.
 Erythema Nodosum is a panniculitis or inflammation of subcutaneous fat that has multiple associations, one of which is IBD. Red, tender, nodular lesions occur on the anterior tibial area. These lesions follow the course of the intestinal disease.
 Pyoderma Gangrenosum is an ulcerating, tender lesion with a dusky border. It often occurs on the anterior tibial area or around a stoma site. Lesions can progress rapidly. Lesions sometimes follow the course of the intestinal disease, however not always.
4. Hereditary Hemmorrhagic Telangiectasia (HHT) or Osler-Weber-Rendu Syndrome. This disorder is characterized by vascular lesions including telangiectasias and arteriovenous malformations. Such lesions occur in the brain, lung and GI tract. Clinical manifestations include epistaxis and GI bleeding. Numerous telangiectasias occur on the lips.
5. CREST. This syndrome is an acronym for calcinosis, raynauds, esophageal dysfunction, sclerodactyly and telangiactasia. Patients experience dysphagia and reflux symptoms. Calcinosis is a deposition of calcium in the soft tissue, often around the elbows. Raynauds is a discolouration of fingers due to vasospasm that often results from exposure to cold. In sclerodactyly, the skin of the fingers becomes tightened and waxy. Telangiectasia occur on the chest and back.
6. A number of polyposis syndromes have cutaneous manifestations. Gardner's syndrome is a form of Familial Adenomatous Polyposis, patients develop hundreds to thousands of colonic polyps at a young age. Colon cancer is inevitable without colectomy, generally by age 40. Many patients develop epidermoid cysts of the face, scalp and extremeties. Multiple unerupted supernumerary teeth may be seen.
 Peutz-Jeghers syndrome is characterized by hamartomatous polyps, mucocutaneous hyperpigmentation and an elevated risk of various cancers.
7. Dermatitis Herpetiformis is a prurtitic, vesicular rash. It may be seen on the scalp, shoulders, elbows, knees or buttocks. It is associated with celiac disease. The skin lesions usually respond to the introduction of a gluten free diet.

8.   Cutaneous disorders of liver disease. As noted previously, patients with liver disease may become jaundiced. In cirrhosis, palmar erythema, telangiactasia, and caput medusa (dilated periumbilical veins) may also be seen. Patients with hemochromatosis, a condition of iron overload, may develop a bronze discolouration of the skin. Xanthomas, deposits of yellowish, cholesterol rich material, develop on the trunk and face of patients with primary biliary cirrhosis.

22. Extraintestinal changes seen in patients with GI disease

Provided through the courtesy of Dr. John McKaigney, University of Alberta

Case 1 – Scleroderma

Case 2 - Peutz-Jegher's syndrome

Case 3 - Crohn disease

37

Case 4 - Osler-Weber-Rendu
Licorice, Fungal infection, Post antibiotic
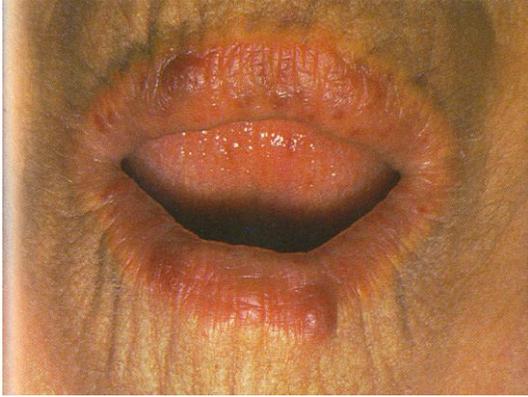
Case 5 - Black Tongue—Bismuth

Case 6 - Canker Sores and Angular Cheilosis
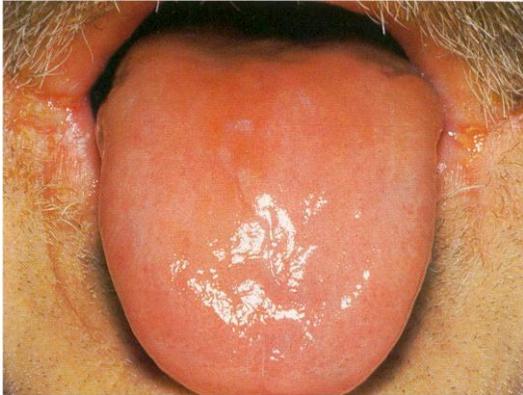
Case 7 – Syphylis
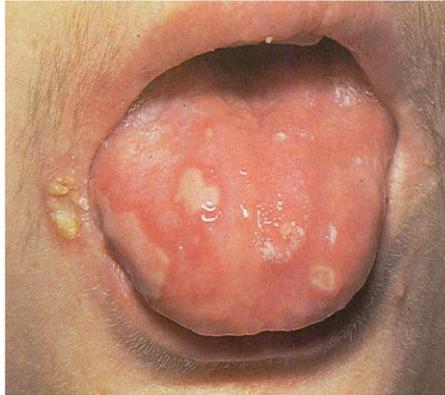
Case 8 – Macroglossia
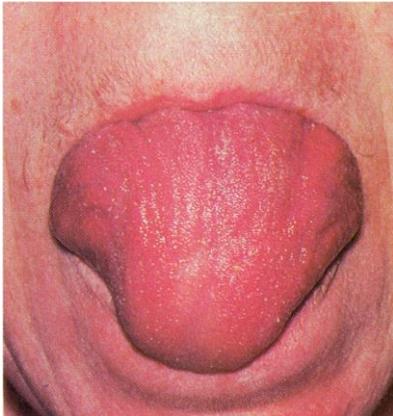
Case 9 - Behçet'ssyndrome—Oral and genital ulceration

Case 10 - Anterior uveitis

Case 11 – Xanthelasmata

Case 12 – Dermatomyositis

Case 13 - Acanthosis nigricans

Case 14 - Spider angioma syndrome

Case 15 - Blue rubber bleb nevus

Case 16 - Leukocytoclastic vasculitis

Case 17 - Dermatitis herpetiformis

Case 18 - Cullen's sign hemorrhage

Case 19 - Grey Turner's sign—Flank again in acute pancreatitis

Case 20 - Erythema nodosum

Case 21 - Pyoderma gangrenosus

Case 22 - Ascitic abdomen with caput medusa type veins and umbilical hernia

Case 23 - Caput medusa

Case 24 - Skin pigmentation —hemochromatosis

Case 25 – Carotenemia

Case 26 - Palmar erythema
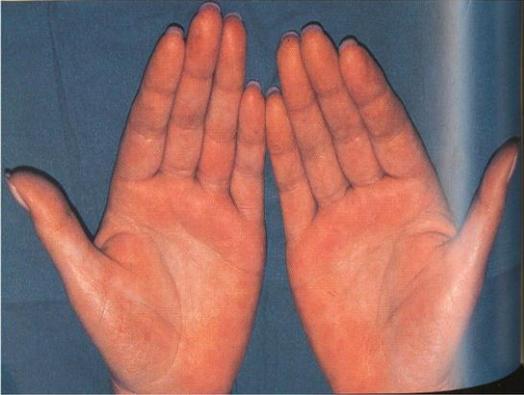
Case 27 – Dupuytrens

Case 28 - White nails

Case 29 - Beau's lines

Case 30 - Nail pitting-psoriasis

Case 31 - Psoriatic Nails

Case 32 - Calcinosis crest syndrome

Case 33 – Scleroderma

Chapter 2: Esophagus

*W.G. Paterson, S. Mayrand and
C.D. Mercer*

1. Introduction

The esophagus is a hollow muscular organ whose primary function is to propel into the stomach the food or fluid bolus that it receives from the pharynx. Symptoms of esophageal disease are among the most commonly encountered in gastroenterology. Fortunately, most symptoms are due to benign disease that can be easily remedied. The physician must be on the lookout, however, for the more serious disorders, which can present with a similar spectrum of symptoms. This chapter will focus on the pathophysiology, diagnosis and management of the more common esophageal disorders. Rare diseases involving the esophagus will be dealt with only briefly.

2. Anatomy

2.1. Muscular Anatomy

The esophagus is a hollow muscular tube closed proximally by the upper esophageal sphincter (UES) and distally by the lower esophageal sphincter (LES). The UES consists predominantly of the cricopharyngeus and the caudal fibers of the inferior pharyngeal constrictor muscles. The UES forms a transverse slit at the C5–C6 vertebral level due to surrounding bony structures and cartilage. In the proximal one-quarter to one-third of the esophagus, the muscle is striated. There is then a transition zone of variable length where there is a mixture of both smooth and striated muscle. The distal one-half to one-third of the esophageal body and LES are composed of smooth muscle. The LES is located at the junction between the esophagus and stomach, usually localized at or just below the diaphragmatic hiatus. With careful dissection, the LES can be identified as an area of thickened circular smooth muscle consisting of two components, namely, semi-circular "clasp" fibers on the lesser curvature, and "sling-like" muscle bundles on the greater curvature that merge with the long oblique gastric muscle fibers.

2.2. Innervation

The motor innervation of the esophagus is via the vagus nerves. The cell bodies of the vagal efferent fibers innervating the UES and the proximal striated-muscle esophagus arise in the nucleus ambiguus, whereas fibers destined for the distal smooth-muscle segment and the LES originate in the dorsal motor nucleus. The esophagus and LES also receive sympathetic nerve supply (both motor and sensory) arising from spinal segments T1–T10. Sensory innervation is also carried via the vagus and consists of bipolar nerves that have their cell bodies in the nodose ganglion and project from there to the brainstem.

2.3. Blood Supply

Arterial blood supply to the UES and cervical esophagus is via branches of the inferior thyroid artery. Most of the thoracic esophagus is supplied by paired aortic esophageal arteries or terminal branches of bronchial arteries. The LES and the most distal segment of the esophagus are supplied by the left gastric artery and by a branch of the left phrenic artery. Venous drainage is via an extensive submucosal plexus that drains into the superior vena cava from the proximal esophagus and into the azygous system from the mid-esophagus. In the distal esophagus, collaterals from the left gastric vein (a branch of the portal vein) and the azygos interconnect in the submucosa. This connection between the portal and systemic venous systems is clinically important; when there is portal hypertension, variceal dilation can occur in this area. These submucosal esophageal varices can be the source of major gastrointestinal hemorrhage.

2.4. Lymphatic Drainage

In the proximal third of the esophagus, lymphatics drain into the deep cervical lymph nodes, whereas in the middle third, drainage is into the superior and posterior mediastinal nodes. The distal-third lymphatics follow the left gastric artery to the gastric and celiac lymph nodes. There is considerable interconnection among these three drainage regions.

2.5. Histology

The wall of the esophagus consists of mucosa, submucosa and muscularis propria. Unlike other areas of the gut, it does not have a distinct serosal covering, but is covered by a thin layer of loose connective tissue. The mucosa consists of stratified squamous epithelium in all regions of the esophagus except the LES, where both squamous and columnar epithelium may coexist. Beneath the epithelium are the lamina propria and the longitudinally oriented muscularis mucosa. The submucosa contains connective tissue as well as lymphocytes, plasma cells and nerve cells (Meissner's plexus). The muscularis propria consists of an inner circular and an outer longitudinal muscle layer. The circular muscle layer provides the sequential peristaltic contraction that propels the food bolus toward the stomach. Between the circular and longitudinal muscle layers lies another nerve plexus called the myenteric or Auerbach's plexus, which mediates much of the intrinsic nervous control of esophageal motor function.

3. Physiology

The major function of the esophagus is to propel swallowed food or fluid into the stomach. This is carried out by sequential or "peristaltic" contraction of the esophageal body in concert with appropriately timed relaxation of the upper and lower esophageal sphincters. The esophagus also clears any refluxed gastric contents back into the stomach and takes part in such reflex activities as vomiting and belching.

3.1. Deglutition: Primary Peristalsis

The act of deglutition is a complex reflex activity. The initial phase is under voluntary control. Food is chewed, mixed with saliva and formed into an appropriately sized bolus before being thrust to the posterior pharynx by the tongue. Once the bolus reaches the posterior pharynx, receptors are activated that initiate the involuntary phase of deglutition. This involves the carefully sequenced contraction of myriad head and neck muscles. The food bolus is rapidly engulfed and pushed toward the esophagus by the pharyngeal constrictor muscles. Simultaneously there is activation of muscles that lift the palate and close off and elevate the larynx in order to prevent misdirection of the bolus. Almost immediately upon activation of this reflex, the UES opens just long enough to allow the food bolus to pass through; it then rapidly shuts to prevent retrograde passage of the bolus. The oropharyngeal phase is thus completed and the esophageal phase takes over. This involves two major phenomena: (1) the sequential contraction of the circular muscle of the esophageal body, which results in a contractile wave that migrates toward the stomach; and (2) the relaxation and opening of the LES, which allows the bolus to pass. The peristaltic sequence and associated UES and LES relaxation induced by swallowing are termed *primary peristalsis*. These can be assessed manometrically using an intraluminal tube to measure pressures. The typical sequence seen during primary peristalsis is depicted in Figure 1. *Secondary peristalsis* refers to a peristaltic sequence that occurs in response to distention of the esophagus. This is a localized peristaltic wave that usually begins just above

the area of distention. It is associated with LES relaxation, but not with UES relaxation or deglutition.

3.2. Upper Esophageal Sphincter Function

The UES serves as a pressure barrier to prevent retrograde flow of esophageal contents and the entry of air into the esophagus during inspiration. This high pressure zone is created by tonic contraction of the UES muscles, which is produced by tonic neuronal discharge of vagal lower motor neurons. With deglutition this neuronal discharge ceases temporarily and permits relaxation of the UES. UES opening will not occur with relaxation of the muscles alone; it requires elevation and anterior displacement of the larynx, which is mediated by contraction of the suprahyoid muscles. Relaxation lasts for only one second and is followed by a post-relaxation contraction (Figure 1).

3.3. Esophageal Body Peristalsis

There is a fundamental difference in the control mechanisms of peristalsis between the upper (striated-muscle) esophagus and the lower (smooth-muscle) esophagus. In the striated-muscle segment, peristalsis is produced by sequential firing of vagal lower motor neurons so that upper segments contract first and more aboral segments subsequently. In the smooth-muscle segment, the vagal preganglionic efferent fibers have some role in the aboral sequencing of contraction, but intrinsic neurons are also capable of evoking peristalsis independently of the extrinsic nervous system. Transection of vagal motor fibers to the esophagus in experimental animals will abolish primary peristalsis throughout the esophagus; however, in this setting, distention-induced or secondary peristalsis will be maintained in the smooth-muscle but not in the striated-muscle segment. Furthermore, if vagal efferent fibers are stimulated electrically (Figure 2), a simultaneous contraction will be produced in the striated-muscle esophagus that begins with the onset of the electrical stimulus, lasts throughout the stimulus, and ends abruptly when the stimulus is terminated. In the smooth-muscle esophagus, however, the response to vagal efferent nerve stimulation is quite different, in that the onset of contractions is delayed relative to the onset of the stimulus. The latency to onset of the contraction increases in the more distal segments of the esophagus (i.e., the evoked contractions are peristaltic).

This experimental observation indicates that intrinsic neuromuscular mechanisms exist and can mediate peristalsis on their own. Further evidence for this mechanism is found in studies where strips of esophageal circular smooth muscle are stimulated electrically in vitro. The latency to contraction after stimulation is shortest in the strips taken from the proximal smooth-muscle segment and increases progressively in the more distal strips.

This latency gradient of contraction is clearly important in the production of esophageal peristalsis. Although the exact mechanisms are unclear, initial or deglutitive inhibition is important. With primary or secondary peristalsis, a wave of neurally mediated inhibition initially spreads rapidly down the esophagus. This is caused by the release of the inhibitory neurotransmitter nitric oxide, which produces hyperpolarization (inhibition) of the circular smooth muscle. It is only after recovery from the initial hyperpolarization that esophageal muscle contraction (which is mediated primarily by cholinergic neurons) can occur. Thus, the duration of this initial inhibition is important with respect to the differential timing of the subsequent contraction. Derangements of the mechanisms behind this latency gradient lead to nonperistaltic contractions and dysphagia. Such derangements could result from problems with either the intrinsic neural mechanisms (enteric nervous system) or the central neuronal sequencing.
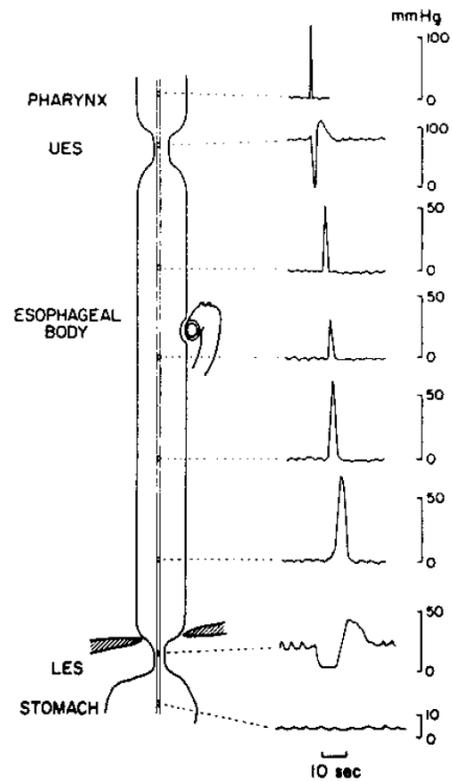
Figure 1. Schematic representation of primary peristalsis as recorded by intraluminal manometry. Swallowing is marked by a rapid pharyngeal contraction coincident with abrupt relaxation of the UES. This is followed by postrelaxation contraction of the UES and sequential contraction of the esophageal body, which produces a pressure wave that migrates toward the stomach. A swallowed food bolus is pushed in front of this migrating contraction wave. The LES relaxes within 1 to 2 seconds of the onset of swallowing and remains relaxed until the esophageal pressure wave has reached the distal esophagus. LES pressure then recovers and is followed by a postrelaxation contraction, which occurs in continuity with the distal esophageal contraction.

Source: Goyal RK, Paterson WG. Esophageal motility. In: Wood JD (ed.), Handbook of physiology: motility and circulation, vol. 4. Washington, DC: American Physiological Society, 1989. Used with permission.
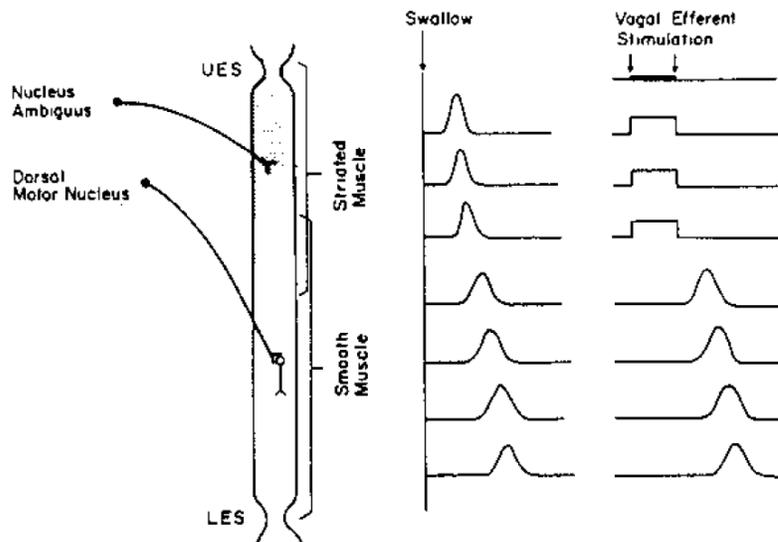
Figure 2. Schematic representation of esophageal peristaltic contractions as evoked by swallowing and vagal efferent nerve stimulation. Swallowing evokes sequential esophageal contractions that pass smoothly from the striated- to the smooth-muscle segment. Electrical stimulation of the distal cut end of a vagus nerve, which simultaneously activates all vagal efferent fibers, evokes peristaltic contractions only in the smooth-muscle segment of the esophagus. In the striated-muscle esophagus, vagal stimulation causes simultaneous contractions that occur only during the period of stimulation. This demonstrates that the striated-muscle esophagus is dependent on central neuronal sequencing for its peristaltic contraction, whereas intrinsic neuronal mechanisms are capable of producing a persistaltic sequence in the smooth-muscle segment.

Source: Goyal RK, Paterson WG. Esophageal Motility. In: Wood JD (ed.), Handbook of physiology: motility and circulation, vol. 4. Washington, DC: American Physiological Society, 1989. Used with permission.

3.4. Lower Esophageal Sphincter Function

The LES is an intraluminal high-pressure zone caused by tonic contraction of a region of physiologically distinct circular smooth muscle at the junction of the esophagus and stomach. This results in a pressure barrier that separates the esophagus from the stomach and serves to prevent reflux of gastric contents up into the esophagus. In normal individuals, resting LES pressure averages between 10 and 35 mmHg above intragastric pressure. Patients with very feeble resting LES pressure are prone to develop gastroesophageal reflux disease (GERD). Unlike that of the UES, the resting tone of the LES is primarily due to myogenic factors that result in tonic contraction of the sphincter. Extrinsic innervation as well as circulating hormones can modify the resting tone; however, the muscle fibers themselves have inherent properties that result in their being tonically contracted.

At the time of deglutition or when the esophagus is distended, the LES promptly relaxes. Swallow-induced LES relaxation is mediated by vagal efferent fibers that synapse on inhibitory neurons of the myenteric plexus. The predominant inhibitory neurotransmitter released from these intrinsic neurons is nitric oxide. LES relaxation usually lasts about five to seven seconds, and is sufficient to abolish the gastroesophageal pressure barrier. This permits the food bolus to pass unimpeded from the esophagus to the stomach. The LES also relaxes to permit belching or vomiting. Inadequate LES relaxation is seen in achalasia and results in dysphagia.

4. Symptoms and Signs of Esophageal Diseases
4.1. Symptoms
4.1.1. Dysphagia

The sensation of food sticking during swallowing is a manifestation of impaired transit of food through the mouth, pharynx or esophagus. It is important to differentiate oropharyngeal ("transfer") dysphagia from esophageal dysphagia. If the patient has problems getting the bolus out of the mouth, then one can be certain of an oropharyngeal cause; if the food sticks retrosternally, an esophageal cause is indicated. Some patients, however, will sense food sticking at the level of the suprasternal notch when the actual obstruction is the distal esophagus. Thus, it can be difficult to determine the site of the problem when patients refer their dysphagia to the suprasternal notch or throat area. With these patients it is important to elicit any ancillary symptoms of oropharyngeal-type dysphagia, such as choking or nasal regurgitation. It may also be helpful to observe the patient swallowing in an attempt to determine the timing of the symptom; with esophageal dysphagia referred to the suprasternal notch, the sensation of dysphagia onsets several seconds after swallowing begins.

The history can also be used to help differentiate structural from functional (i.e., motility disorders) causes of dysphagia. Dysphagia that is episodic and occurs with both liquids and solids from the outset suggests a motor disorder, whereas when the dysphagia is initially for solids such as meat and bread, and then progresses with time to semisolids and liquids, one should suspect a structural cause (e.g., stricture). If such a progression is rapid and associated with significant weight loss, a malignant stricture is suspected. Associated symptoms help determine the etiology of dysphagia. For instance, a reflux-induced stricture should be suspected if the dysphagia is associated with heartburn or regurgitation, esophageal cancer if there is associated mid-back pain and weight loss, a motor disorder such as diffuse esophageal spasm if there is angina-like chest pain, and a "scleroderma esophagus" if there is arthralgia, skin changes or Raynaud's phenomenon.

4.1.2. Odynophagia

This refers to the sensation of pain on swallowing. Local inflammation or neoplasia in the mouth and pharynx can produce such pain. When the pain is retrosternal, one should suspect nonreflux-induced forms of esophagitis, such as infection, radiation or pill-induced (chemical) injury. Less commonly it occurs with esophageal cancer, a deep esophageal ulcer (e.g., Barrett's ulcer) or esophageal motor disorders.

4.1.3. Heartburn or Pyrosis

The sensation here is one of retrosternal burning. Typically it begins in the low retrosternal area and radiates up to the throat. It may be precipitated by bending over or lying down, and usually begins shortly after consuming certain foods or beverages. It is often associated with

regurgitation of acidic material into the back of the throat. "Heartburn" with these features indicates gastroesophageal reflux. This very common symptom has been experienced at one time or another by over one-third of the population and therefore does not necessarily indicate serious disease. Many patients will complain of "heartburn," but this should not be taken at face value: this term is used by some patients to describe unrelated symptomatology. It is therefore important to have patients describe exactly what they mean by the term *heartburn*.

4.1.4. Regurgitation

This refers to the spontaneous appearance of food or fluid in the back of the throat or in the mouth. Some patients describe this symptom as "vomiting"; therefore it is important to determine whether there is associated nausea, retching, etc., when patients present with "vomiting." The taste and consistency of the regurgitated material is an important historical detail. Regurgitation of acidic or bile-stained fluid indicates gastroesophageal reflux. Regurgitation of undigested food or stagnant fluid devoid of an acidic taste indicates an esophageal transport problem (e.g., achalasia). (With achlorhydria, such as occurs with pernicious anemia, gastric contents also lack acid.) In motor disorders and mechanical obstruction of the esophagus, food may become stuck and then rather quickly will be regurgitated if it does not pass through into the stomach. Some patients regurgitate food back into their mouths after a meal only to chew and swallow it all over again. This is called *rumination* and, although a rarity in humans, it is a normal physiological event in certain animals.

4.1.5. Nonheartburn Chest Pain

This may also be an indication of esophageal disease. Chest pain, and in particular mid-dorsal pain, is seen in advanced esophageal cancer. The most common type of nonheartburn esophageal chest pain, however, is a pain that is qualitatively similar to the pain of ischemic heart disease (so-called "noncardiac chest pain"). This pain can be squeezing or crushing and can radiate into the jaw or arms. Unlike ischemic heart pain, angina-like chest pain of esophageal origin is not predictably elicited by exertion and often occurs spontaneously, in relationship to meals or in the middle of the night. It may be associated with other more typical esophageal symptoms. Clearly, patients with this type of pain need to have ischemic heart disease excluded. Once this is done, many will be found to have either gastroesophageal reflux or some form of esophageal motor or sensory disorder.

4.1.6. Waterbrash

The sudden appearance of copious amounts of saliva in the mouth must be differentiated from regurgitation of fluid. With waterbrash, acid reflux into the esophagus stimulates hypersalivation via a (cholinergic) neural reflex.

4.1.7. Bleeding

This may be a symptom of certain esophageal diseases. Mucosal laceration in the region of the gastroesophageal junction (*Mallory-Weiss tear*), as a consequence of retching or vomiting, is a common cause of upper gastrointestinal tract bleeding. Esophageal varices can cause massive hematemesis and melena. Deep esophageal ulcers may also bleed massively, but this is uncommon. Usually the bleeding from ulcerative lesions of the esophagus or esophageal cancer is occult. When the patient does present with hematemesis or melena from esophagitis, the rate of bleeding is usually slow; therefore, significant hemodynamic compromise is uncommon.

4.1.8. Respiratory/Laryngeal Symptoms

These may be a manifestation of esophageal disease or oropharyngeal swallowing disorders. Aspiration at the time of swallowing will cause coughing, choking and eventual hoarseness. In addition, patients with motor disorders or gastroesophageal reflux disease (GERD) may regurgitate esophageal or gastric contents up into the larynx and subsequently aspirate. These patients may present with pneumonia, chronic cough, wheezing, hoarseness or laryngitis. Gastroesophageal reflux might also trigger coughing and wheezing via a vagovagal reflex.

4.2. Signs

It is uncommon for esophageal disease to be associated with specific physical findings. Signs of weight loss and malnutrition can be found if the esophageal problem is so severe that adequate caloric intake is not maintained. There may be signs of metastatic disease (e.g., hepatomegaly, supraclavicular lymphadenopathy) in esophageal cancer. Patients with GERD rarely have respiratory tract signs such as wheezing, hoarseness or lung consolidation. It is important to look for signs of connective tissue disease (especially scleroderma) in patients with reflux symptoms or dysphagia.

The physical examination is more often helpful in patients with oropharyngeal dysphagia. Careful examination of the head and neck for structural and neurologic abnormalities is mandatory. It is also important to look for more generalized neurologic or connective tissue abnormalities. Observing the patient swallow is also useful when oropharyngeal dysphagia is present.

5. Investigations Used in the Diagnosis of Esophageal Disease

A number of tests are available to facilitate the diagnosis of patients with suspected esophageal disease. The choice of which diagnostic test to use depends on the patient presentation and the question(s) to be answered.

5.1. Barium X-ray

This most commonly used method of investigating the esophagus evaluates both structural lesions and motor disorders. It is most useful in evaluating patients with dysphagia. Proper communication between physician and radiologist is vital. Videotaping the barium swallow ("video-fluoroscopy swallowing study") allows for playback and slow-motion review. This is very helpful in assessing the rapid events of the oropharyngeal phase of swallowing. Use of marshmallows, barium-coated cookies and different consistencies of barium further assesses swallowing disorders, as delays in transport may not be apparent with simple liquid barium. The disadvantage of barium x-rays is that they are relatively insensitive in detecting mucosal disease. If a patient is suspected of having an esophageal perforation, a water soluble contrast agent (Gastrograffin) should be used in place of barium.

5.2. Endoscopy with Mucosal Biopsy and Brush Cytology

Fiberoptic endoscopy directly visualizes the esophageal mucosa as well as other areas of the upper gastrointestinal tract. Its direct view is superior to barium x-rays for assessing mucosal disease of the esophagus. Furthermore, pinch biopsies and/or brush cytology of specific lesions are easily obtained through the endoscope. Microscopic evidence of esophagitis may be found even when the mucosa looks grossly normal. Endoscopy is the single most useful test in the evaluation of patients with reflux symptoms, as it permits one to establish the presence or

absence of esophagitis (Figure 3) or Barrett's esophagus (Section 7.3). Endoscopy gives little reliable information regarding esophageal function.

5.3. Endoscopic Ultrasound

This technique combines ultrasonography with endoscopy by placing an ultrasound transducer at the end of a video endoscope. It is particularly useful in staging esophageal cancer in that it is the most sensitive imaging technique for determining the depth of invasion through the esophageal wall and involvement of region lymph nodes.
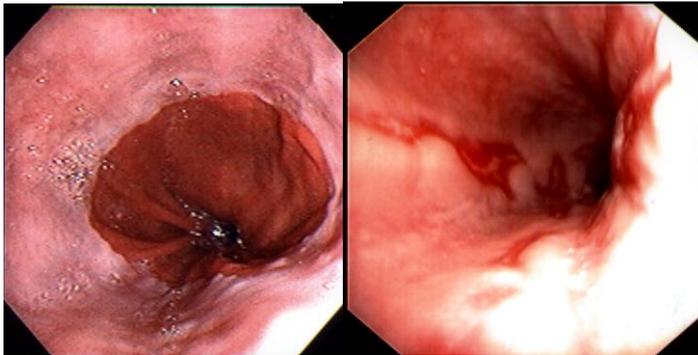
Figure 3. Endoscopic view of normal distal esophagus (left) and from a patient with reflux esophagitis (right). Note linear superficial ulcerations with normal appearing esophageal mucosa in between.

5.4. Esophageal Manometry

This involves recording intraluminal pressures at multiple sites along the esophagus (Figure 1). The most commonly used method involves a perfused multilumen catheter bundle with side holes at 5 cm intervals. Each catheter is connected to a pressure transducer, which in turn is attached to a physiograph. LES pressure and swallow-induced LES relaxation are measured, as are pressure responses to swallowing at several esophageal sites. Pharyngeal peristalsis and UES function can also be measured. Esophageal manometry is the "gold standard" in the assessment of esophageal motor disorders. Motor dysfunction, however, may be intermittent and therefore not detected at the time of the study. Manometry may be combined with provocative tests (acid perfusion, balloon distention and/or pharmacological stimulation of the esophagus with bethanechol or edrophonium) in an attempt to evoke abnormal contractions and reproduce the patient's chest pain (Section 11). In recent years, the introduction of "high resolution" manometry has allowed for more detailed recording and analysis of esophageal motor function. Using multiple pressure sensors spaced at 1 cm intervals, the pressure profile from pharynx to stomach can be assessed simultaneously. Sophisticated software converts the data to contour plots using different colours to depict pressure variations, thereby facilitating detection of motor disorders. The technique can be combined with simultaneous intraluminal impedance recording, so that bolus transit can be simultaneously measured and correlated with motor function. This powerful methodology enhances the detection of esophageal motor disorders, but is quite expensive.

5.5. Ambulatory Esophageal pH Monitoring

This is performed using a pH electrode passed via the nose into the distal esophagus, which continuously records intraluminal pH over a 24-hour period. Acid reflux events can be identified by an abrupt drop in pH to < 4. The results of this test are compared to a healthy control population to determine whether an abnormal degree of gastroesophageal acid reflux is present. The test is most useful, however, in determining whether atypical symptoms coincide with acid reflux events (Figure 4), and in objectively assessing the response to therapy in patients with refractory symptoms. Recently, wireless pH electrodes, which are clipped to the distal esophageal mucosa endoscopically, have been introduced. These are better tolerated and allow for longer recording intervals (e.g. 48-72 hours), which increases diagnostic yield. In addition, combined pH and impedance recording catheters are being used at some centres, and are useful in detecting non-acid or weakly acidic reflux events that may be responsible for refractory symptoms in a small subset of patients.
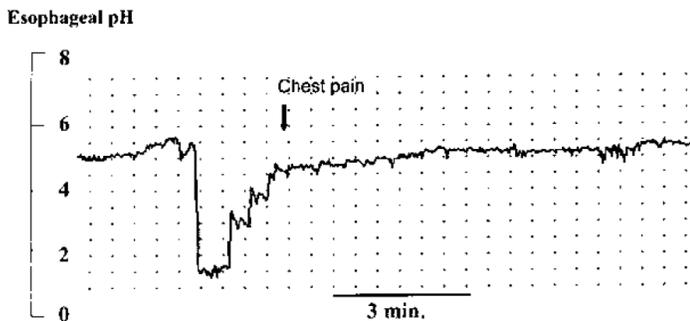
Figure 4. Extract from an intraesophageal 24-hour pH study in a patient with unexplained chestpain. Note that intraluminal pH abruptly drops, indicating a gastroesophageal acid reflux event. This is followed shortly thereafter by the patient's recording chest pain.
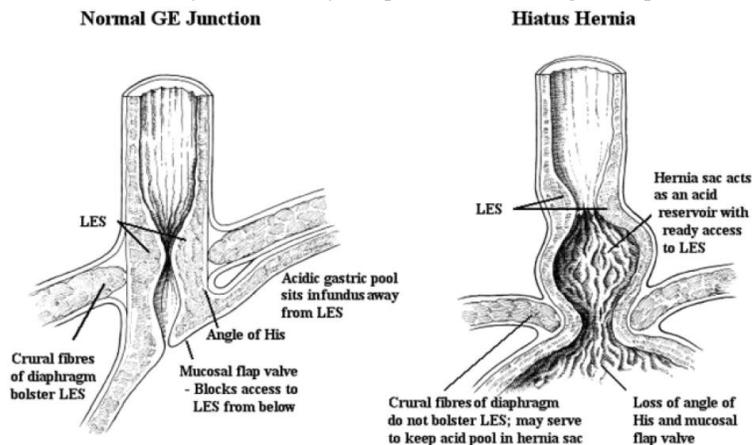
Figure 5. Sliding hiatus hernia (right) in comparison to normal anatomy of the gastroesophageal junction (left). Also depicted are the various mechanisms whereby a hiatus hernia can predispose to GERD. (Reproduced from Paterson WG, Zhang Y. The lower esophageal sphincter. Clinical & Investigative Medicine, 2002; 25; 47-53, with permission.)

6. Anatomic Variants

6.1. Congenital Anomalies

Embryologically the gastrointestinal and respiratory tracts start out as a single tube; however, by the second month of gestation they have completely divided. Problems with this process lead to various congenital anomalies, the most common being tracheoesophageal fistula with esophageal atresia. In 85–90% of cases, the proximal esophagus ends in a blind pouch while the distal esophagus consists of a blind pouch in continuity with the stomach. Neonates with this abnormality develop immediate aspiration with feeding. There is no air in the bowel on x-ray films of the abdomen, contrary to what is observed in those with fistulas involving the distal esophagus. In 1–2% of cases there is an "H-type" fistula with atresia. The patient presents with repeated pulmonary infections and abdominal distention. The latter is caused by air getting into the gastrointestinal tract via the fistula when the infant cries. Because the H-type fistula may be very small, the condition may go unnoticed until adulthood, when it is detected during the investigation of recurrent pulmonary infections. Some of these fistulas may close spontaneously but produce paraesophageal inflammation and ultimately localized esophageal stricture formation.
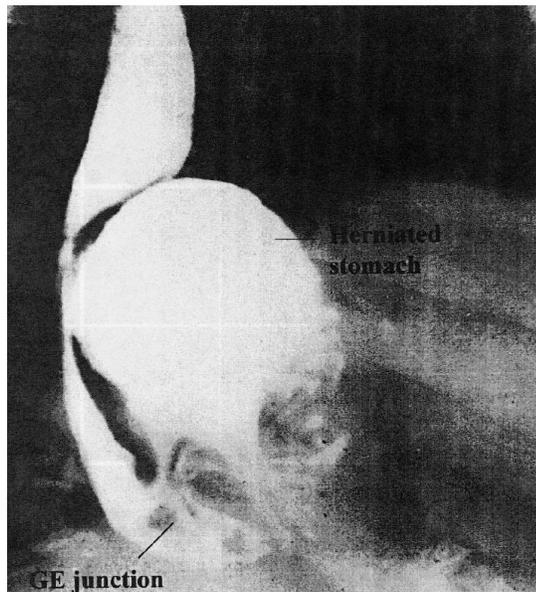
Figure 6. Barium contrast study of a paraesophageal-type hiatus hernia. Note that unlike in a sliding hiatus hernia depicted in Figure 5, the gastroesophageal (GE) junction has maintained its normal position at the hiatus, but a large portion of the gastric fundus has migrated up through the hiatus alongside the distal esophagus. The herniated portion of the stomach is compressing the distal esophagus.

Treatment of esophageal fistulas (with or without atresia) is surgical. The prognosis is now quite good and mortality is usually related to coexistent congenital malformations. It is important to remember that many of these patients will have gastroesophageal reflux as well as abnormal esophageal peristalsis following surgery, which may cause significant long-term problems.

Congenital esophageal stenosis is a rare anomaly that is also probably related to abnormal differentiation of the gastrointestinal and respiratory tracts, as resected specimens have been found to have pulmonary epithelium and/or bronchial remnants. Sequestered pulmonary remnants with connections to the esophagus but not associated with stenosis have also been described.

6.2. Hiatus Hernia

The majority of hiatus hernias are acquired. Rarely, a hiatus hernia can be caused by a congenitally short esophagus. Hiatus hernias can be divided into two types: (1) sliding and (2) paraesophageal (Figures 5 and 6, respectively). A *sliding hiatus hernia* refers to the condition where a circumferential cuff of cardia and proximal stomach migrates up through the diaphragmatic hiatus and into the thorax. This may reduce and reform spontaneously. These hernias are very common and increase in incidence with advancing age. Generally they are of no clinical significance, despite the fact that many patients and physicians persist in attributing a wide variety of symptoms to them. Large hiatus hernias may be associated with iron deficiency anemia that is presumably caused by recurrent superficial ischemic ulcerations at the site where the diaphragm exerts pressure on the herniated stomach ("Cameron's" ulcers). If no other source of GI blood loss is discovered after thorough investigation, and patients continue to be iron-deficient despite supplementation and antiulcer treatment, surgical correction of the hernia should be performed.

The etiology of the sliding hiatus hernia is obscure. Certainly there is laxity and dilation of the diaphragmatic hiatus and associated laxity of the phrenoesophageal ligament; however, these may well be secondary and not primary pathophysiologic factors. In some cases, persistent gastroesophageal reflux may result in inflammation and consequent esophageal shortening, which in turn leads to the development of a hiatus hernia.

A sliding hiatus hernia is often seen in association with GERD; the precise role of the hernia in the pathogenesis of the reflux remains uncertain. The majority of people with hiatus hernias do not have significant reflux disease, and occasionally patients with severe reflux esophagitis will not have a hiatus hernia. It appears that a hiatus hernia may contribute to gastroesophageal reflux (see Figure 5), but it is most unlikely that this is the prime etiologic factor. A hiatus hernia may contribute to GERD by providing a reservoir of gastric acid that has ready access to the distal esophagus whenever the LES relaxes.

Paraesophageal hiatus hernias are uncommon. These consist of the fundus of the stomach migrating through the hiatus alongside the esophagus without any displacement of the gastroesophageal junction. Although these hernias may be asymptomatic, many surgeons believe that they should be treated surgically when the diagnosis is made because the herniated portion may become strangulated and infarcted. However, a recent study suggests that observation alone is a valid option. Paraesophageal hernias may also cause dysphagea by compressing the distal esophagus (Figure 6). The treatment consists of reduction of the herniated stomach into the abdomen, elimination of the hernia sac and closure of the herniated defect by reapproximating the crura. Whether or not an anti-reflux procedure (i.e. fundoplication) should be added is debatable. On occasion, both types of hiatus hernias can coexist in the same patient (mixed hiatus hernia).

7. Gastroesophageal Reflux Disease (GERD)

GERD is the most common condition to affect the esophagus, with roughly 5 million Canadians experiencing heartburn or acid regurgitation, the cardinal symptoms of GERD, at least

once per week. The disease spectrum ranges from patients with heartburn and other reflux symptoms without morphologic evidence of esophagitis (the so-called endoscopy-negative reflux disease) to patients with deep ulcer, stricture or Barrett's epithelium. Everyone has some degree of gastroesophageal reflux; it becomes pathological only when associated with troublesome symptoms or complications. Fortunately, the vast majority of patients suffering from GERD have an easily controlled disorder. At the other end of the spectrum, there are patients who develop severe damage to the esophagus. Some will develop Barrett's metaplasia as a consequence of gastroesophageal reflux, which in turn predisposes them to adenocarcinoma.

7.1. Pathophysiology

GERD results from the reflux of gastric contents into the esophageal lumen. Early pathogenesis concepts focused on anatomic factors: reflux was considered a mechanical problem, related to the development of a hiatus hernia. We now know, however, that a hiatus hernia can occur without GERD, and conversely, GERD can occur without a hiatus hernia. Many factors are involved in the pathogenesis of GERD.

7.1.1. Barriers to Gastroesophageal Reflux

By far the most important barrier to gastroesophageal reflux is the LES. Factors such as the intra-abdominal location of the sphincter, extrinsic compression exerted by the diaphragmatic crura and the angle of His (which forms a "mucosal flap valve") may augment this barrier but plays a less significant role than the LES itself (Figure 5). Some patients developing reflux esophagitis have feeble LES tone, but in most, resting LES pressure is normal or only slightly impaired. Gastroesophageal reflux occurs by three major mechanisms, as outlined in Figure 7.
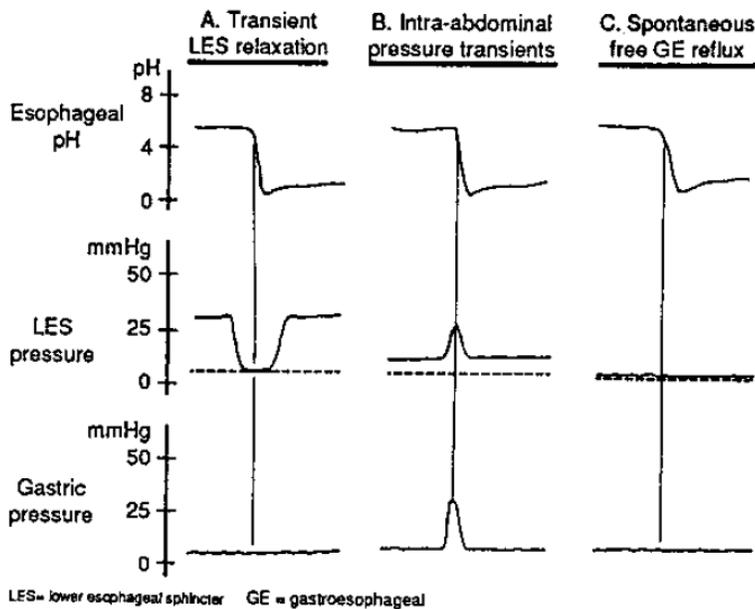
Figure 7. Schematic representation of three different mechanisms of gastroesophageal (GE) reflux.
A. Transient LES relaxation refers to the sudden occurrence of LES relaxation that causes obliteration of the gastroesophageal pressure barrier and permits gastric contents to reflux up into the esophagus. The reflux event is marked by the sudden drop in esophageal pH. These transient LES relaxations are sometimes related to incomplete or failed peristalsis but may also occur in isolation.

B. Intra-abdominal pressure transients are sudden increases in intragastric pressure caused by coughing, sneezing or deep inspiration. The increased intragastric pressure overcomes the LES pressure and results in reflux.

C. Spontaneous free reflux occurs when there is very low or nonexistent LES pressure, which permits spontaneous reflux across the gastroesophageal junction. In healthy volunteers without GERD, virtually all reflux episodes are due to transient LES relaxation. In patients with reflux esophagitis, approximately two-thirds of the reflux episodes are due to transient LES relaxation. The remaining one-third are caused by either intra-abdominal pressure transients or spontaneous free gastroesophageal reflux.

Source: Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. The New England Journal of Medicine1982; 307:1547–1552. Used with permission.

7.1.2. Esophageal Clearance

Once reflux occurs, the duration of insult to the esophageal mucosa depends on the rapidity with which the esophagus clears this material. Once the initial (primary) peristaltic wave has passed, the bolus (a portion of which frequently remains) is cleared by one or two secondary peristaltic waves. The remaining small adherent acidic residue is then neutralized by saliva, which is carried down by successive swallows. Disorders of salivation or esophageal motor function will impair this clearance mechanism and predispose to the development of GERD. Patients with severe GERD may have frequent prolonged nighttime reflux episodes because during sleep, peristalsis seldom occurs and salivary flow virtually ceases. Hence the contact time of refluxed material with the esophagus is markedly increased.

7.1.3. Gastroduodenal Factors

In some patients delayed gastric emptying further predisposes to the development of GERD. Bile salts and pancreatic enzymes, if refluxed back into the stomach, can in turn reflux into the esophagus and may inflict worse damage than when gastric juice is refluxed alone. Such reflux into the stomach and then the esophagus may be significant after gastric surgery, when the pylorus is destroyed. Whenever there is increased gastric pressure or an increase in gastric contents, there is greater likelihood that reflux will occur when the sphincter barrier becomes deficient. Furthermore, distention of the proximal stomach is a potent stimulus for transient LES relaxation via a vago-vagal reflex.

7.1.4. Mucosal Resistance

The degree of damage to esophageal mucosa depends not only on the composition of the refluxed material and the amount and duration of reflux, but also on defensive factors within the mucosa itself. These include protective secretions from esophageal glands, the integrity of tight junctions between adjacent epithelial cells and esophageal blood flow. Certain patients are more susceptible to the development of actual mucosal damage, for reasons that are not clear.

7.2. Clinical Features

Most patients present with heartburn and acid regurgitation that onset after eating certain foods or following various postural maneuvers (e.g., bending over, lying flat). Frequency varies from once a week or less to daily episodes with disruption of sleep. Other presenting symptoms include waterbrash, angina-like chest pain, dysphagia and various respiratory symptoms

(hoarseness, throat discomfort, cough, wheezing). The dysphagia may be due to the development of a reflux-induced stricture, loss of compliance of the esophageal wall secondary to inflammation, or to abnormal motility induced by the refluxed acid. Odynophagia is rarely a symptom of GERD and should alert the physician to another diagnosis such as infectious esophagitis.

Reflux symptoms are common during pregnancy because of increased intra-abdominal pressures and the LES-relaxant effect of progesterone. Physical examination in patients with GERD rarely reveals associated physical signs. In severe cases with stricture formation there may be weight loss secondary to decreased caloric intake. Patients with GERD secondary to scleroderma may have the physical findings associated with this disease.

7.3. Diagnosis

In the vast majority of patients, GERD can be diagnosed from the history alone and treated without further investigation. Some specialists believe that all patients with longstanding symptomatic gastroesophageal reflux should undergo endoscopy. The argument in favour of this approach is that Barrett's esophagus will be found in about 5-10% of patients with GERD symptoms for more than 5 years. This identifies those at increased risk for the development of adenocarcinoma (Section 7.5.2). Such an approach is of unproven benefit, however, and is almost certainly not cost-effective. Less than half the patients undergoing endoscopy for reflux symptoms will have erosive esophagitis. The remainder have non-erosive reflux disease ("NERD"). Endoscopic biopsy in these patients may detect microscopic evidence of esophagitis (hyperplasia of the basal zone layer, elongation of the papillae, inflammatory cell infiltration, dilated intercellular spaces).

In patients with atypical or multiple symptoms, or typical symptoms that don't respond to empiric treatment, a 24-hour pH reflux study may be necessary to establish that the symptom(s) are in fact due to acid reflux (Figure 4). It is important to first rule out ischemic heart disease if the presenting symptom is angina-like chest pain. In general, patients who present with symptoms of complicated GERD (i.e., dysphagia, bleeding or respiratory symptoms) require investigation. If dysphagia is present, an upper GI endoscopy, with or without initial barium x-ray study, should be performed. It may be reasonable to forgo further testing in patients with heartburn and dysphagia that completely resolve with proton pump inhibitor therapy.

Esophageal manometry has little role to play in the routine assessment of patients with GERD. It may be useful in the assessment of patients with atypical chest pain, and can be combined with an acid perfusion (Bernstein) test as well as with other provocative tests. It is recommended that manometry be performed prior to surgical intervention, because patients with significant underlying motor disorders of the esophagus (e.g., scleroderma) often develop severe dysphagia following an antireflux procedure.

7.4. Treatment

7.4.1. Medical Treatment

The treatment of GERD is directed toward the abnormal pathophysiology. The ideal therapeutic agent would be one that restores barrier function of the gastroesophageal junction. Unfortunately, at present there are no pharmacological agents that are capable of doing this well. The GABAB receptor agonist baclofen has been shown to decrease the frequency of transient LES relaxations and thereby reduce GE reflux. This drug is limited by side effects and is not yet approved for use in GERD. Prokinetic agents can increase LES pressure and improve gastric

emptying and esophageal clearance, but unfortunately these drugs have fairly limited efficacy in the treatment of GERD. The one showing the most promise (cisapride) has been withdrawn from the market because of cardiac side effects.

Because of these limitations, acid suppression remains the main pharmacological approach to the treatment of GERD. It is well documented that acid and pepsin (if in an acid milieu) are the predominant constituents of refluxed gastric juice that damage the esophageal mucosa. Over the counter antacids and alginates in liquid or tablet form can alleviate heartburn symptoms when taken on an as-needed basis, and are commonly used by patients as self-medication.

Both histamine-2 receptor antagonists and proton pump inhibitors have been shown to improve symptoms and heal reflux esophagitis. The efficacy of the proton pump inhibitors is far superior to histamine-2 receptor antagonists in this regard, therefore these agents have become the mainstay of treatment for reflux disease. With a once or twice daily proton pump inhibitor treatment regimen, one can expect symptom resolution and/or healing of esophagitis in over 90% of patients.

Although the level of evidence for efficacy is not strong, certain lifestyle modifications should be considered in the management of GERD. Elevating the head of the bed on 4"-6" blocks and avoiding sleeping in the right lateral position have been shown to decrease nocturnal acid exposure. These maneuvers should be considered in patients with nocturnal reflux symptoms. Avoiding specific foods, drugs or activities may also help. Reflux is more likely to occur after large, fatty meals, especially if the patient becomes recumbent too soon after food ingestion. Certain drugs with smooth muscle-relaxing effects (e.g., calcium channel blockers, nitrates and drugs with anticholinergic effects) can decrease resting LES pressure or delay gastric emptying, and therefore may exacerbate GERD. Obesity also predisposes to GERD, therefore weight loss should be encouraged in obese patients.

GERD is a chronic relapsing condition that usually requires long-term treatment. As a general rule the physician should use the simplest, least expensive and least potent therapeutic regime that will keep the patient's symptoms in check.

7.4.2. Antireflux Surgery

Although several different surgical procedures have been used to treat GERD, the most popular one is the "Nissen fundoplication," originally described by the Swiss Rudolf Nissen in 1955 (Figure 8). Some expert surgeons have reported that this 360-degree gastric wrap can produce long-term control of reflux symptoms in > 90% of patients. However, more recent reports suggest that reflux symptoms eventually recur in up to 30% of patients. The Nissen fundoplication was first performed laparoscopically in 1991, and when compared to the open procedure, this approach results in reduced postoperative pain, hospital stay and recovery period, with similar functional outcome. Surgical therapy improves the LES barrier and is recommended for patients with proven gastroesophageal reflux whose symptoms respond inadequately to medical therapy, or who cannot or will not take the required medication. Ideal patients for the Nissen fundoplication are young and have an incompetent LES with normal esophageal peristaltic contraction amplitude, esophagitis documented by endoscopy and/or endoscopic biopsy and 24-hour esophageal pH monitoring demonstrating frequent reflux. Patients who should not be considered for surgical therapy include those who refuse testing, have certain primary esophageal motility disorders, have not responded initially to a trial of proton pump inhibitors, or who have normal 24-hour pH tests.
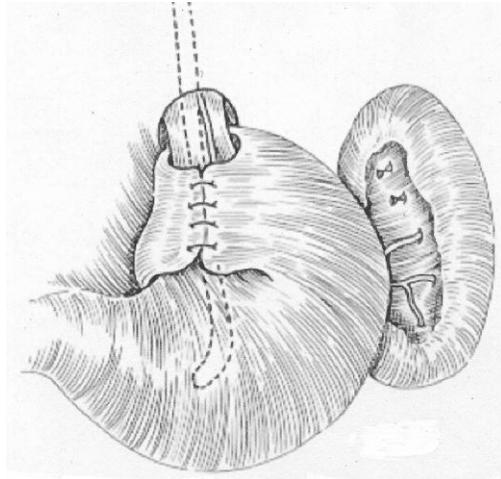
Figure 8. Diagram of completed Nissen fundoplication. The hiatus hernia is reduced into the abdomen and the fundus of the stomach wrapped around the distal esophagus. This serves to bolster the pressure barrier at the gastroesophageal junction and change the anatomy in such a way that the acid pool no longer accumulates near the LES. Spleen is seen on right.

Careful diagnostic evaluation is required in all patients prior to antireflux surgery. Endsocopy determines the presence and severity of esophagitis and excludes Barrett's esophagus, while 24-hour esophageal pH monitoring objectively documents the frequency and duration of reflux and ensures that pathological reflux is present and responsible for the patient's symptoms. pH monitoring is a particularly important test in those patients who do not have endoscopic evidence of esophagitis. Manometry identifies the location and tone of the LES and rules out primary motility disorders of the esophagus, which might contraindicate an anti-reflux operation.

The principles of the operation are to: (1) reduce and fix the LES into the positive pressure environment of the abdomen; (2) augment the LES pressure; and (3) close the diaphragmatic hiatus around the esophagus to prevent the wrap from migrating into the chest postoperatively. Obesity, very large paraesophageal hiatal hernias, shortened esophagus and re-do antireflux surgery are relative contraindications to laparoscopic anti-reflux surgery, particularly early in a surgeon's laparoscopic career. Overall operative mortality for first-time operations is ≤ 0.5%. Between 10 and 20% of patients develop significant problems with dysphagia and/or gas-bloat symptoms after surgery. Inability to belch or vomit may also occur. In most cases these problems resolve with time.

7.5. Complicated GERD
7.5.1. Peptic Stricture

Chronic GERD may lead to peptic stricture formation (Figure 9). This is a fibrous stricture related to collagen deposition that occurs in the course of repair of esophagitis. Patients are usually asymptomatic until the luminal narrowing has reached 12–14 mm. At this point dysphagia to solids occurs. As the stricture progresses, the dysphagia gradually progresses to semisolids and then liquids. Treatment of peptic strictures involves peroral dilation, using either mercury-filled rubber bougies, rigid dilators passed over guidewires, or balloons passed through
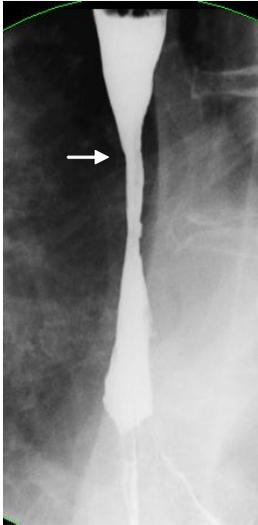
endoscopes. In close to 50% of patients one or two dilation sessions prove adequate, and no further dilations are required because ongoing medical treatment of the reflux is successful. In others, the stricture recurs and periodic dilations are required to maintain luminal patency. In patients who are otherwise healthy, consideration should be given to antireflux surgery if frequent dilations are required to maintain luminal patency. The success rate of antireflux surgery is lower in such patients with peptic stricture. Strictures are less likely to recur following dilation if the patient is treated with a proton pump inhibitor. For this reason, long-term treatment with a proton pump inhibitor is indicated in patients with peptic stricture.

Figure 9. Barium swallow radiograph in a patient with a tight peptic stricture (arrow).

7.5.2. Barrett's Esophagus

In this condition the squamous epithelium of the distal esophagus is replaced by columnar epithelium with intestinal metaplasia (Figure 10). Deep ulcers as well as strictures at the new squamocolumnar junction may also develop. Severe hemorrhage may complicate the deep ulcers. This condition occurs in approximately 10% of patients with chronic GERD, although recent prospective studies in which careful biopsies were performed from the region of the gastroesophageal junction suggest that the incidence is may be higher.
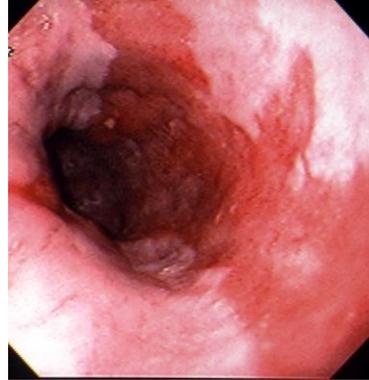
Figure 10. Endoscopic appearance of Barrett's esophagus. Note that broad tongues of columnar-type epithelium extend up from the gastroesophageal junction into the esophageal body that is normally lined with squamous epithelium. Histology reveals an intestinal-type metaplasia with goblet cells.

Barrett's epithelium is a premalignant condition. At the time of initial presentation, up to 10% of patients found to have Barrett's esophagus will have coexistent adenocarcinoma arising in the Barrett's epithelium. This number gives an exaggerated impression of the magnitude of risk, because Barrett's esophagus patients with cancer are more likely to seek medical attention. The true incidence of adenocarcinoma developing in Barrett's epithelium is only about 1 case for every 200 patient-years of follow-up. This nevertheless represents about a 30- to 40-fold increase over the risk faced by the general population. For this reason current guidelines recommend that periodic (i.e., every 2-3 years) endoscopy and mucosal biopsy should be performed in order to detect precancerous lesions or early cancer. Most patients will develop severe dysplasia before

frank invasive carcinoma occurs. Thus, if patients are found to have severe dysplasia or early mucosal carcinoma, esophageal resection should be considered in order to prevent the development of invasive carcinoma. Recently, photodynamic therapy, radiofrequency ablation and endoscopic mucosal resection have been introduced as effective, less invasive alternatives to surgery in patients with severe dysplasia or intramucosal carcinoma complicating Barrett's esophagus.

7.5.3. Respiratory Complications

In some patients the refluxed gastric contents may get past the UES and into the larynx and lungs. This may produce asthma, recurrent chest infections, chronic cough and laryngitis. In addition, gastroesophageal reflux may trigger broncho-spasm or cough via a neural reflex. GERD with aspiration is more commonly seen in the pediatric age group; when present, antireflux surgery should be performed unless there is a well-documented response to medical therapy.

8. Nonreflux-Induced Esophagitis

8.1. Infectious Esophagitis

Bacteria rarely cause primary esophageal infection, although the esophagus can be involved secondarily by direct extension from the lung. The two most common forms of infectious esophagitis are caused by Candida and herpes viruses. Other viruses (e.g., CMV, HIV) and fungi can also cause esophagitis; however, this is uncommon and almost invariably associated with immunosuppression.

8.1.1. Candida Esophagitis

This is by far the most common form of infectious esophagitis. Usually there is a predisposing cause, such as diabetes mellitus, recent antibiotic therapy or some form of immunocompromise. The patient may be asymptomatic. Not all patients will have associated oral thrush. More commonly, however, patients present with odynophagia, retrosternal chest pain and/or dysphagia. Severe cases can be complicated by bleeding, a stricture and sinus tract formation with secondary lung abscess. Barium x-rays may reveal an irregular granular or even cobblestone appearance to the esophageal mucosa, but in many patients the barium esophagogram is unremarkable; for this reason, endoscopy with biopsy and brushing are required to make the diagnosis. The typical endoscopic appearance is the presence of small raised whitish plaques (Figure 11).
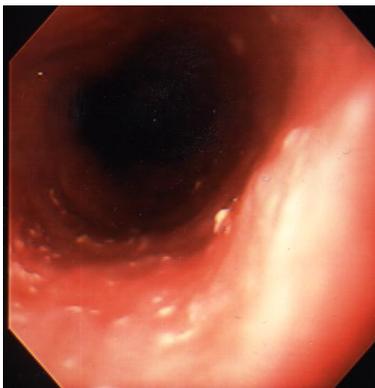
Figure 11. Endoscopic appearance of Candida esophagitis. Note the small white plaques adherent to the esophageal mucosa.

When the plaques are removed the underlying mucosa is seen to be erythematous and friable. Specimens obtained by biopsy or brush cytology should be examined microscopically for the presence of typical Candida yeast with pseudohyphae formation. Mild cases of Candida esophagitis can be treated with oral nystatin (luminal treatment); however, more extensive disease, especially if the patient is immunocompromised, may require systemic treatment with fluconazole. Amphotericin B is required if there is evidence of systemic spread.

8.1.2. Herpes Simplex Esophagitis

Next to Candida, this is the most common form of infectious esophagitis. The clinical presentation is much the same as with Candida esophagitis. There may also be constitutional symptoms of a viral upper respiratory tract infection preceding the esophageal symptoms. Herpetic mouth or skin lesions may also develop. This infection occurs most frequently in immunosuppressed patients, but also develops sporadically in healthy young adults. Endoscopy with biopsy and brush cytology is required to confirm the diagnosis. The pathognomonic finding is the eosinophilic "Cowdry's Type A" intranuclear inclusion body. Herpetic esophagitis is self-limiting in immunocompetent individuals; specific treatment is not indicated. Symptoms of odynophagia often respond to a combination of antacids mixed with viscous Xylocaine®. In severely immunocompromised patients, intravenous acyclovir treatment should be instituted.

8.2. Eosinophilic (Allergic) Esophagitis

In recent years there has been increasing recognition of so-called allergic or eosinophilic esophagitis. It used to be felt that this was largely restricted to the paediatric population, however, adults of all ages are now being diagnosed with this disease. It is most common in young adult men. The typical presentation is recurrent solid food dysphagia and often food bolus obstructions. Barium swallow x-ray and endoscopy may show little or no change. Proximal esophageal strictures or a diffuse small caliber esophagus is a clue to this disease when seen on barium x-ray. Endoscopically (Figure 12) one often sees subtle longitudinal furrowing of the esophageal mucosa, transverse ridges or corrugation or whitish papules or plaques that have the appearance of candida esophagitis. The latter actually represent small eosinophilic abscesses. Another characteristic feature is fragility of the esophageal mucosa, such that bits of mucosa often tear away when passing the endoscope through the esophageal lumen. The diagnosis requires mucosal biopsy, which shows intense infiltration of eosinophils into the squamous mucosa. More than 15 eosinophils per high-powered field confirms the diagnosis.

Although food allergy may trigger this disorder, it is also possible that inhaled allergens may result in indirect involvement of the esophagus as part of the allergic response. It is also possible that swallowed mucus-containing inhaled allergens are responsible. A majority of these patients have a history of allergic disease such as asthma, skin atopy or allergic rhinitis. In general, allergy testing is usually unhelpful. In the paediatric population, exclusion diets and/or elemental diets have been reported to be beneficial. Currently, the preferred treatment in adults is either topical steroids (fluticasone, which is swallowed rather than inhaled) or the leukotriene inhibitor montelukast sodium.
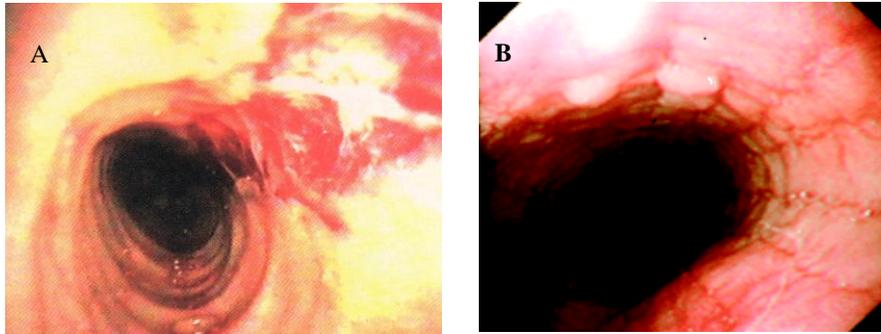
Figure 12. Endoscopic features of eosinophilic esophagitis. A) Note transverse ridges ("trachealization") and mucosal trauma (top right). The latter is caused by trauma from passage of the endoscope, due to mucosal fragility and subtle luminal narrowing. B) Longitudinal furrowing and corrugation.

8.3. Esophagitis Associated with Immune-Mediated Disease

Rarely, esophagitis can occur in association with Crohn disease or Behçet's syndrome. The typical lesion is scattered aphthous-type ulcerations, although severe transmural involvement with stricture formation can occur. The esophagus can also be severely involved in pemphigoid, pemphigus, epidermolysis bullosa and lichen planus. Esophagitis occurs in as many as one-third of patients who develop chronic graft-versus-host disease after bone marrow transplantation. The typical lesion is a generalized epithelial desquamation of the upper and middle esophagus. There may be associated ring-like narrowings or strictures due to submucosal fibrosis. A nonspecific esophageal motor disorder may also develop and result in superimposed reflux esophagitis because of poor esophageal clearing. Sarcoidosis also rarely causes esophageal inflammation.

8.4. Chemical-Induced Esophagitis
8.4.1. Caustic Chemical Ingestion

Strong acids or alkalis ingested accidentally or as a suicide attempt cause marked esophagitis. Alkali tends to be more injurious to the esophageal mucosa than acid and produces liquefaction necrosis as well as thermal burns (due to heat release when the alkali is hydrated by gut secretions). Acids tend to produce superficial coagulation necrosis and eschar formation. Typically the patient develops immediate chest pain and odynophagia. Oral burns also may produce local pain and drooling. There may be respiratory symptoms such as stridor, dyspnea and hoarseness if the airway is contaminated. Symptoms alone do not permit accurate prediction of the presence or absence of esophageal injury; therefore early diagnostic endoscopy should be considered in most patients. Clearly, endoscopy should not be performed if there is evidence of esophageal perforation. In the management of these patients, it is imperative to maintain an adequate airway. Oral intake must be stopped and intravenous fluids administered. Empiric treatment classically has involved antibiotics and corticosteroids, but there is no good evidence documenting the efficacy of this approach. Patients who survive the acute phase of the injury are at risk of developing strictures because of the intense collagen deposition associated with healing. This often requires repeated esophageal dilation to maintain luminal patency.

Lye-induced injury increases the risk of developing squamous cell carcinoma of the esophagus. Typically there is a 30- to 50-year lag time before the development of cancer. For this reason any patient with previous lye injury and new esophageal symptoms should be promptly investigated. The extent of the risk is such that most experts do not recommend periodic endoscopic surveillance.

8.4.2. Pill-Induced Esophagitis

A large number of oral agents can cause localized esophageal injury. The antibiotic doxycycline and the anticholinergic emepronium bromide are two of the most common culprits. Nonsteroidal anti-inflammatory drugs and slow-release forms of potassium chloride are also frequently implicated. Patients with this type of injury typically take their medication with a small amount of water and then immediately lie down to go to bed. They may then wake up several hours later with severe retrosternal chest pain and odynophagia. Capsules and tablets are notorious for being transported through the esophagus quite poorly unless adequate amounts of fluid are ingested at the same time. This is an important point to remember in counselling all patients who take medicines at bedtime. Rarely, the medication becomes lodged and causes a deep esophageal ulcer with perforation. More commonly the ulceration is superficial and heals in a few weeks. Late stricture formation may occur. Patients with esophageal motility disorders are particularly prone to this complication. The bisphosphonate alendronate sodium has also been reported to rarely cause esophageal ulceration, but the mechanism of this injury is unclear.

8.5. Radiation-Induced Esophagitis

When included in the field of irradiation, the esophagus becomes inflamed in up to 80% of patients receiving therapeutic radiation for cancer. The risk of esophagitis is greater if there is concomitant chemotherapy. The patients typically develop chest pain, dysphagia and odynophagia shortly after the initiation of therapy. This can be a serious problem in such patients, who are often already severely malnourished. Late stricture formation is a well recognized complication.

9. Disorders of the Oropharyngeal Phase of Deglutition

A variety of structural and functional disorders can disrupt the oropharyngeal phase of deglutition and result in oropharyngeal or "transfer"-type dysphagia (Table 1). In the assessment of these patients it is important to exclude disorders for which specific treatment is available. The most important investigation is a carefully performed video fluoroscopic study of the swallowing mechanism. In addition to the usual barium studies, it is helpful to observe deglutition when the patient swallows barium soaked cookies or bread. Not only will this examination identify and characterize disorders of oropharyngeal coordination, it will also help exclude structural lesions. If an inflammatory, neoplastic or other structural lesion is suspected, direct or indirect laryngoscopy is indicated. At present, manometric studies of the pharynx and UES add little to what can be learned from radiologic studies.

Ideally, treatment of oropharyngeal motor disorders should be directed at the underlying disease. Frequently this is not possible, and nonspecific treatment must be instituted. In some cases reassurance and education are all that is required. Many patients will be able to control their symptoms simply by eating slowly and carefully in a relaxed atmosphere. In patients in whom aspiration develops because of inadequate clearing of the hypopharynx after the initial swallow, it is beneficial to have the patient immediately follow a "bolus" swallow with a second,

"dry" swallow. Correcting denture problems and avoiding foods of certain consistency may also help. Speech-language pathologists have special expertise as swallowing therapists and can be very helpful in the management of these patients.

A *normal* tracing is on the left and depicts sequential "peristaltic" contractions in the esophageal body with full LES relaxation. *Hypertensive peristalsis* or *"nutcracker" esophagus* is characterized by normal peristalsis and LES relaxation, but the amplitude of contraction in the distal esophagus is abnormally high (> 180 mmHg). In *diffuse esophageal spasm*, normal peristaltic waves are interspersed with high-pressure, nonpropulsive (simultaneous) contraction waves and are often repetitive. The resting LES pressure may be abnormally high, but swallow-induced LES relaxation is normal. In *achalasia* there is complete absence of normal peristalsis in the smooth-muscle esophagus (simultaneous contractions only) and swallow-induced LES relaxation is either absent or incomplete. Note also that resting intraesophageal pressures are elevated. *Scleroderma* is characterized by the presence of weak, nonperistaltic esophageal contractions and a markedly hypotensive LES that relaxes normally with swallowing.

For patients in whom these simple measures are not helpful and whose symptoms are such that respiratory and nutritional complications are developing, cricopharyngeal myotomy is sometimes performed. This helps patients with true cricopharyngeal achalasia or Zenker's diverticulum (Section 13). Unfortunately, the response to myotomy is inconsistent in most other patients with oropharyngeal dysphagia, because inadequate opening of the UES is rarely due to dysfunction of the cricopharyngeal muscle alone. More often there is associated weakness of the suprahyoid muscles, which actually open the sphincter, and/or associated problems with pharyngeal peristalsis. Cricopharyngeal myotomy does little to improve such altered physiology. Once cricopharyngeal myotomy has been performed, the patient has lost an important defense mechanism against the aspiration of refluxed material. The patient should therefore be instructed to elevate the head of his or her bed on blocks in order to minimize this risk. For this same reason patients with severe GERD should not undergo cricopharyngeal myotomy unless the reflux can be controlled.

Table 1. Classification of disorder causing oropharyngeal dysphagia

➢ Central nervous system disease
  o Cerebrovascular accident (brainstem, pseudobulbar palsy)
  o Wilson's disease
  o Amyotrophic lateral sclerosis
  o Brainstem neoplasm
  o Tabes dorsalis
  o Parkinson's disease

➢ Peripheral nervous system disease
  o Bulbar poliomyelitis
  o Miscellaneous peripheral neuropathies
  o Head and neck neoplasms
  o Past-radical neck surgery

- Muscle disease
  - Muscular dystrophy
  - Polymyositis and dermatomyositis
  - Metabolic myopathy (e.g., hypo- and hyperthyroidism)
  - Amyloidosis
  - Systemic lupus erythematosus
  - Myasthenia gravis

- Local disorders
  - Oropharyngeal inflammation
  - Oropharyngeal neoplasms
  - Zenker's diverticulum

- Idiopathic conditions
  - Cricopharyngeal achalasia
  - Idiopathic oropharyngeal incoordination

When all other measures fail and nutritional and respiratory complications develop, a gastrostomy feeding tube should be placed.

10. Motor Disorders of the Esophagus and Lower Esophageal Sphincter

Esophageal motor disorders can be classified as either primary or secondary. Primary disorders refer to those that usually affect the esophagus alone and have no known etiology. Secondary disorders are motility derangements caused by some other systemic or local condition. Examples of secondary disorders include acid-reflux-induced dysmotility, dysmotility related to the neuropathy associated with diabetes and motor dysfunction secondary to esophageal involvement in scleroderma or other connective tissue disorders. The well-defined primary motor disorders include the hypertensive peristaltic or "nutcracker" esophagus, diffuse esophageal spasm and achalasia (Figure 13).
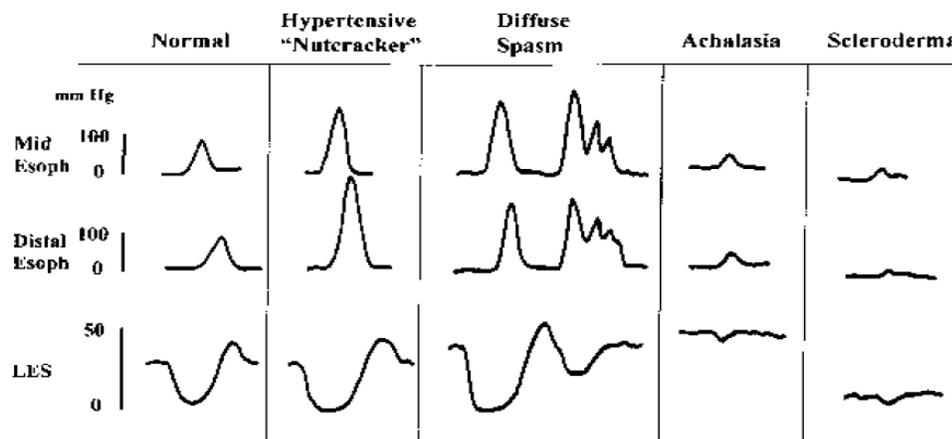
Figure 13. Schematic representation of manometric features of the major esophageal motor disorders.

Many cases of primary motility disorders are actually "nonspecific," having a variety of abnormalities that do not fulfill criteria established for the well-defined esophageal motor disorders. Patients with primary motor disorders typically present with dysphagia and/ or chest pain. The pain is often qualitatively similar to angina pectoris and has been classically attributed to smooth-muscle spasm. However, recent studies have suggested that the pain may be secondary to a lowered sensory threshold to esophageal stimuli such as distention or acid. Some patients with motor disorders will have secondary GERD because of poor clearing or poor LES function. Here, heartburn and regurgitation may be prominent symptoms. The diagnosis of a motor disorder can be made on the basis of history and barium swallow x-ray and endoscopy. If there is dysphagia referred to the retrosternal area and no evidence of a structural lesion or inflammatory disease on x-ray or endoscopy, then by exclusion the patient's dysphagia is likely related to a motor disorder. As mentioned previously, the quality of the dysphagia (e.g., sporadic, unpredictable dysphagia to both liquids and solids) is also helpful in differentiating motor disorders from structural causes of dysphagia. During fluoroscopy, the radiologist is usually able to detect abnormalities of motor function as the barium is swallowed. The use of a solid bolus, such as a piece of bread soaked in barium, may be helpful in diagnosing esophageal rings or webs. Endoscopy primarily rules out secondary causes of the disorder (i.e., reflux or eosinophilic esophagitis and neoplasm). In order to define specifically the type of motor disorder present, however, esophageal motility studies are required. The manometric features of the important esophageal motor disorders are depicted schematically in Figure 9.

10.1. "Nutcracker" Esophagus

This motility disorder is characterized by normally propagated but high amplitude peristaltic waves in the distal esophagus. The duration of the contraction wave is also often prolonged. LES relaxation is normal, although in many patients the resting LES pressure is elevated. Patients often present with angina-like chest pain and usually do not complain of dysphagia. Nutcracker esophagus is the most frequent abnormal manometric finding in patients referred for evaluation of noncardiac angina-like chest pain. The etiology is unknown. Rarely, this disorder progresses to diffuse esophageal spasm or even vigorous achalasia. Reassurance that the pain is not cardiac but is secondary to a benign esophageal condition is the most important part of treatment. Nitrates and calcium channel blockers (to relax smooth muscle) have been used extensively, but have no proven benefit. Tricyclic antidepressant drugs are effective in alleviating the pain in these patients, presumably because of their effect on visceral sensation. In some patients with nutcracker esophagus, pain is actually triggered by acid reflux; these patients often respond dramatically to appropriate antireflux therapy.

10.2. Diffuse Esophageal Spasm

This is characterized by normal peristalsis interspersed with frequent high pressure nonpropagated or "tertiary" waves and multipeaked waves. Patients often present with dysphagia and chest pain. In advanced diffuse esophageal spasm, the x-ray will show a corkscrew pattern (Figure14) as different segments of the esophagus vigorously and simultaneously contract. The etiology is obscure, but may relate to degenerative changes in the intrinsic and extrinsic esophageal nerves. Management involves reassurance and the use of nitrates or calcium channel blocking agents. Injection of Botulinum toxin into the muscle of the LES or distal esophagus also appears to be effective in alleviating dysphagia in this condition. Rarely, patients with severe disease unresponsive to medical measures may benefit from a long esophageal myotomy.

Figure 14. Barium contrast X-ray depicting a "Corkscrew" esophagus, typical of diffuse esophageal spasm. Simultaneous contractions at multiple sites along the esophagus create this pattern. A similar X-ray picture may be seen in vigorous achalasia, therefore manometry is required to firmly establish the diagnosis.

10.3. Achalasia

This uncommon primary motility disorder is characterized by aperistalsis in the body of the esophagus and absent or incomplete LES relaxation in response to swallowing. Resting LES pressures may also be elevated. Failure of LES relaxation leads to progressive proximal dilation of the esophagus with consequent elevated resting intraesophageal pressures. On x-ray the esophagus is dilated, and retained food and fluid may be present. The distal esophagus narrows in a beak-like fashion (Figure 15). This "beak" represents the hypertonic, nonrelaxing LES. In some patients there are associated high amplitude nonperistaltic contractions in the esophageal body, a condition called *vigorous achalasia*. Achalasia is caused by an inflammatory reaction directed against the inhibitory nitric oxide neurons within the esophageal and LES myenteric plexus. Nerve damage may also be found in the vagal nerve trunks and the dorsal motor nuclei, although these are likely secondary to the myenteric plexus damage. The parasite Trypanosoma cruzi, which is endemic in Brazil, can cause achalasia by destroying myenteric neurons (Chagas' disease). Neoplastic disease can also interfere with esophageal and LES nerve function and cause secondary or "pseudo" achalasia. In most cases, however, the cause of the degeneration is unknown. The cardinal symptom of achalasia is dysphagia, although chest pain and even heartburn may be present. The heartburn is usually not due to gastroesophageal reflux. It may be caused by lactic acid formed by fermentation of stagnant esophageal contents. Another common symptom of achalasia is regurgitation of esophageal contents. Patients with achalasia secondary to cancer are typically older and present with rapidly progressive dysphagia and significant weight loss.

Figure 15. Typical barium x-ray in a patient with achalasia. Note that the esophagus is dilated and there is an air-barium meniscus indicative of stasis. At the gastroesophageal junction there is a beak-like narrowing, which is caused by the nonrelaxing LES. The mucosal contour at this narrow area appears normal, which helps distinguish this from a stricture caused by malignancy or reflux disease.

In mild cases of idiopathic achalasia treatment can begin with the use of calcium channel blockers or long-acting nitrates, which have been shown to decrease LES pressure. This is rarely successful in the long term, however. The treatment then usually performed is pneumatic balloon dilation of the LES. This consists of passing a balloon across the sphincter and inflating it rapidly so that the sphincter is forcefully dilated. Pneumatic dilation is successful in alleviating the dysphagia and improving esophageal transport in 60–90% of patients, although repeated dilations are often required to achieve the highest success rate. Patients who do not respond to pneumatic dilation should be treated with Heller myotomy. This consists of a longitudinal incision through the muscle of the LES, which is now done via a laparoscopic approach. Increasingly, laparoscopic Heller myotomy is being offered as first-line therapy in patients with achalasia. Following either pneumatic dilation or Heller myotomy, the patient can develop GERD, because the pressure barrier preventing reflux has been destroyed. This tends to be worse after Heller myotomy and has led some surgeons to perform a modified antireflux procedure at the time of myotomy. Recent studies have found that injection of botulinum toxin into the muscle of the LES can alleviate dysphagia in approximately two-thirds of patients with achalasia. This therapy is limited because the response is not sustained (average duration is approximately one year), but it may be a useful treatment option in elderly patients who would not tolerate the complications of more invasive therapy. Achalasia patients have an increased risk of developing esophageal cancer and need to be carefully evaluated if new esophageal symptoms develop. Unlike Barrett's esophagus, regular endoscopic surveillance is not recommended in achalasia patients.

10.4. Scleroderma Esophagus

Patients with scleroderma frequently have esophageal involvement. This may occur even in the absence of obvious skin and joint involvement, although in such cases, Raynaud's phenomenon is almost always present. The initial event is damage to small blood vessels, which in turn leads to intramural neuronal dysfunction. With time, actual muscle damage and fibrosis occur. This results in a very hypotensive LES, as well as weak, nonpropulsive esophageal contractions. Scleroderma may also involve the stomach and cause delayed gastric emptying. As a result, patients develop gross GERD. They present with heartburn and regurgitation, as well as dysphagia. The dysphagia can be due to poor esophageal propulsion and/or reflux-induced stricture. These patients need very aggressive treatment for GERD, often requiring twice-daily PPI therapy. Because they have very poor peristaltic function, increasing the barrier at the LES with antireflux surgery may markedly worsen the dysphagia.

11. The Esophagus as a Cause of Angina-Like Chest Pain

At least one-third of the patients referred to a cardiologist or admitted to a coronary care unit because of angina-like chest pain will have cardiac causes excluded. Because in most of these patients an alternative etiology is not apparent, they are often labeled as having "noncardiac chest pain." Lack of a specific diagnosis may lead to ongoing anxiety, changes in lifestyle and frequent medical consultations if the patient continues to worry that serious heart disease may be present. In such patients esophageal disease or dysfunction should be considered. The pathophysiology of angina-like chest pain of esophageal origin is poorly understood. In some patients acid reflux is the cause: these patients experience angina-like chest pain under circumstances in which most people would experience heartburn. In others, the pain is caused by abnormal "spastic" contractions of the esophagus that either occur spontaneously or are secondary to acid reflux. These contractions may be confined to the longitudinal smooth muscle layer, therefore would not be detectable using conventional intraluminal manometry. Many of these patients appear to have an abnormal esophageal pain threshold; pain episodes may be triggered by multiple different stimuli that in normal subjects would not be perceived as painful. The diagnostic approach to patients with noncardiac chest pain is controversial. In the past, full esophageal testing was usually recommended, including upper GI endoscopy, esophageal manometry with provocative testing (Figure 16) and/or 24-hour ambulatory esophageal pH monitoring (Figure 4). More recently the value of such testing has been called into question.

Endoscopy is performed primarily to look for evidence of reflux esophagitis, but the diagnostic yield in this setting is low, and a negative result does not rule out acid reflux as a cause of pain. Esophageal manometry with "provocative testing" (e.g., esophageal acid perfusion, balloon distention or administration of muscarinic agonist) may be used in an attempt to reproduce the patient's chest pain and possibly relate it to induced esophageal muscle spasm.
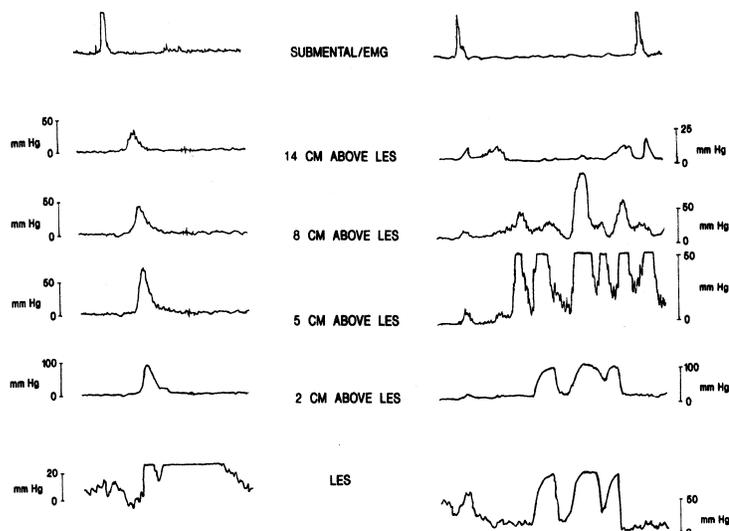
Figure 16. Example of esophageal manometry with provocative testing in a patient with angina-like chest pain and normal coronary angiography. The baseline tracing (left) is within normal limits. During acid perfusion (right) a pattern of diffuse esophageal spasm is induced, which coincided with the patient experiencing her typical angina-like pain. The patient also developed marked esophageal spasm with coincident pain following the injection of bethanechol (not shown). The top tracing is the submental electromyogram (EMG), which records the onset of deglutition. This is followed in sequence by intraluminal side hole pressure recordings from 14, 8, 5 and 2 cm above the lower esophageal sphincter (LES). The lowermost tracing is the pressure recorded by a pressure sensor straddling the LES.

Source: Paterson WG, Marciano-D'Amore DA, Beck IT, et al. Esophageal manometry with provocative testing in patients with non-cardiac angina-like chest pain. Canadian Journal of Gastroenterology1991; 5(2):51–57. Reproduced with permission of the *Canadian Journal of Gastroenterology*.

However, this test appears to lack specificity, as the patient with a positive provocative test may experience seemingly identical spontaneous pain episodes that are unrelated to esophageal dysfunction. Ambulatory 24-hour pH monitoring can be extremely useful in correlating pain episodes with reflux events, but patients must have frequent (i.e., daily) pain attacks if one is likely to be captured during the monitoring period. Because GERD is probably the most common, specifically treatable cause of noncardiac chest pain, it has been recommended that these patients first receive intensive treatment for GERD (i.e., twice-daily proton pump inhibitor therapy). If symptom resolution occurs, then a diagnosis of reflux-induced pain can be presumed and the patient managed accordingly. More in-depth esophageal testing can then be reserved for those patients who fail this empiric therapy and have persisting troublesome pain, especially if associated with considerable anxiety surrounding the diagnosis. Management of angina-like chest pain of esophageal origin should be directed at the specific pathophysiological process. If the pain is

triggered by gastroesophageal reflux, then antireflux treatment may be quite helpful. If the pain is due to esophageal spasm, smooth-muscle relaxants such as nitrates and calcium channel blockers may help, although few controlled clinical trials have demonstrated any significant benefit. Tricyclic antidepressants in relatively low dosage have been shown to be beneficial and should be tried in patients with frequent pain episodes that are not caused by reflux or severe esophageal spasm. These are most likely to be useful in patients with abnormal visceral nociception, or the so-called irritable esophagus. Simple reassurance and education are probably the most important part of treatment. Symptoms often improve once the patient is given a positive diagnosis and no longer fears that underlying heart disease is the cause.

12. Esophageal Neoplasms

A large number of different tumors can involve the esophagus (Table 2). The vast majority are extremely rare and often do not produce clinical disease.

Table 2. Classification of esophageal tumors

➢ Benign tumours
- o Epithelial origin
  - − Squamous cell papilloma
- o Non-epithelial origin
  - − Leiomyoma
  - − Granular cell tumor
  - − Hemangioma
  - − Lymphangioma

➢ Malignant tumors
- o Epithelial origin
  - − Squamous cell carcinoma
  - − Adenocarcinoma
  - − Adenoid cystic carcinoma
  - − Mucoepidermoid carcinoma
  - − Adenosquamous carcinoma
  - − Undifferentiated carcinoma; small-cell carcinoma
- o Non-epithelial origin
  - − Leiomyosarcoma
  - − Carcinosarcoma
  - − Malignant melanoma
- o Secondary tumors
  - − Malignant melanoma
  - − Breast carcinoma

➢ Tumor-like lesion
- o Fibrovascular polyp
- o Heterotopia
- o Congenital cyst
- o Glycogen acanthosis

Carcinoma of the esophagus is a relatively uncommon malignancy in Canada, with only 3 to 4 new cases per 100,000 population per year in males and just over 1 new case per 100,000 population per year in females. Nevertheless, because of its poor prognosis, esophageal cancer ranks among the 10 leading causes of cancer death in Canadian men 45 years of age and older. Although several different types of primary and secondary malignancies can involve the esophagus (Table 2), squamous cell carcinoma and adenocarcinoma are by far the most common esophageal malignancies.

12.1. Adenocarcinoma

Adenocarcinoma used to make up approximately 10% of all esophageal cancers. However, its incidence has been increasing in recent decades such that now it comprises up to 40–60% of esophageal cancers in North America. Rarely, primary esophageal adenocarcinomas arise from embryonic remnants of columnar epithelium or from superficial or deep glandular epithelium. In most instances, adenocarcinoma arises from metaplastic Barrett's epithelium in the distal esophagus (Figure 17). Adenocarcinoma of the cardia of the stomach may also involve the distal esophagus and give the appearance that the cancer arises from the esophagus.

The true incidence of Barrett's-related cancer is uncertain, but most studies suggest that patients with Barrett's esophagus will develop adenocarcinoma at a rate of about 0.5% per year. This is a significant problem given the large number of reflux patients with Barrett's metaplasia. Because dysplasia develops prior to frank carcinoma in Barrett's epithelium, current guidelines recommend that these patients should undergo surveillance endoscopy with multiple biopsies every 2-3 years to identify those who are likely to progress to cancer (Section 7).

The clinical presentation and diagnostic evaluation of patients with adenocarcinoma of the esophagus are similar to those of squamous cell carcinoma (Section 12.2.2). Neoadjuvant therapy with concomitant radiation and chemotherapy followed by surgical resection of the esophagus has a 13% absolute benefit in survival at 2 years versus surgery alone. Surgical resection may be performed with curative intent. However, surgical resection for palliation, or palliation with laser, photodynamic therapy, peroral dilation and/or stent placement are more often required, since curative surgery is feasible in only 20% of patients. The prognosis is similar to that for gastric adenocarcinoma – i.e., an overall five-year survival rate of < 10%.

Table 3. Esophageal squamous cell carcinoma: possible factors

- o Alcohol
- o Tobacco
- o Nutritional exposure
  - − Nitrosamines: "bush teas" containing tannin and/or diterpene phorbol esters
- o Nutritional deficiencies (riboflavin, niacin, iron)
- o Chronic esophagitis
- o Achalasia
- o Previous lyle-induced injury
- o Tylosis
- o Plummer Vinson (Paterson-Kelly) syndrome

12.2. Squamous Cell Carcinoma

The occurrence of squamous cell carcinoma of the esophagus shows striking geographic variability, with high frequencies in certain regions of Iran, Africa, China and the former USSR. This has led to several theories concerning certain environmental agents that may be important etiologically (Table 3). In North America, squamous cell carcinoma is associated with alcohol ingestion, tobacco use and lower socioeconomic status. It is also significantly more common in blacks and in males.

Characteristically these cancers, similarly to adenocarcinoma, extend microscopically in the submucosa for substantial distances above and below the area of the gross involvement. They also have a propensity to extend through the esophageal wall and to regional lymphatics quite early. Furthermore, they usually produce symptoms only when they have become locally quite advanced. For these reasons approximately 95% of these cancers are diagnosed at a time when surgical cure is impossible.

In most studies, the mid-esophagus is the most common site of origin; however, others have reported distal cancers to be most common. The lungs, liver and bones are the most common sites of distant metastases.

Most patients present with progressive, predictable dysphagia and weight loss. Other symptoms include odynophagia, chest pain (which may radiate to the mid-scapular region), hoarseness (due to recurrent laryngeal nerve involvement) and blood loss. Pulmonary complications due to either direct aspiration or esophagorespiratory fistulas are also quite common during the course of the disease. Physical examination is usually negative aside from signs of weight loss. Hepatomegaly or enlarged cervical or supraclavicular lymph nodes may be detected in cases of disseminated metastases.

Barium swallow is usually diagnostic, although small cancers can be missed in up to 30% of cases. Endoscopy with multiple directed biopsies combined with brush cytology is required to confirm the diagnosis. This should be followed by careful attempts to stage the disease prior to deciding on therapeutic intervention. CT scan of the thorax and upper abdomen is required to look for local spread and metastasis. Unfortunately the CT scan lacks sensitivity in this regard. Endoscopic ultrasound appears promising in accurately assessing depth of tumor involvement and presence or absence of enlarged mediastinal lymph nodes. PET scanning is useful to delineate lymph nodes positive for metastatic malignancy.
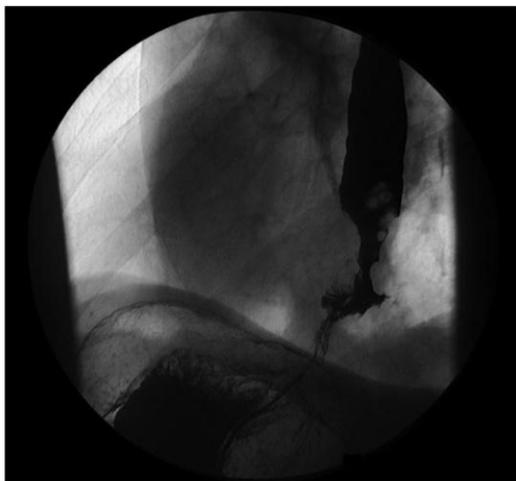
Figure 17. Barium swallow radiograph in a patient with adenocarcinoma of the distal esophagus. Note narrowing of the esophageal lumen with irregular mucosal contour. When similar lesions are in mid or proximal esophagus, they usually are squamous cell cancers. Endoscopic biopsies are required to establish the diagnosis.

Treatment results of squamous cell carcinoma of the esophagus are discouraging. These tumors are quite radiosensitive; however, most centers give radiotherapy to patients who have advanced unresectable tumors or other health problems that make them poor surgical candidates. This understandably leads to very poor overall survival following radiotherapy. In the few reports where radiotherapy is used as the primary mode of therapy in patients who might otherwise be considered surgical candidates, the five-year survival rate is as high as 17%, which compares quite favorably to surgical results. Both forms of treatment have significant morbidity, but the surgical mortality following esophageal resection is 5–10%. Controlled trials are needed, but in only a small proportion of the total population of esophageal cancer patients is cure a realistic goal. In the majority the disease is too far advanced. New regimens that combine radiotherapy and chemotherapy, with or without surgery, are currently being evaluated and show promise in improving cure rates and disease-free survival. However, the toxicity and morbidity from combined treatment can be substantial.

The goal of treatment has to be palliation in most patients. Both radiotherapy and palliative surgery can be used in this setting; however, other modalities are often necessary. The dysphagia can be relieved with peroral dilation, but in many patients this becomes exceedingly difficult as the disease progresses. If this is the case, a prosthetic device can sometimes be placed across the tumor to maintain luminal patency. These stents can work quite well, although tube blockage, tube migration, erosion through the esophageal wall and sudden massive aspiration are important complications. These prosthetic devices are the best treatment for an esophagorespiratory fistula. Photodynamic therapy and radiofrequency ablation are two relatively new minimally invasive treatment modalities for palliating esophageal cancer. The former involves using a photosensitizing compound that accumulates in cancer cells, which leads to their destruction when they are exposed to light of a certain wavelength. The caring physician must also provide emotional support, nutritional support and adequate pain therapy for these unfortunate patients.

13. Miscellaneous Disorders of the Esophagus

13.1. Webs and Rings

Webs are thin, membrane-like structures that project into the esophageal lumen. They are covered on both sides with squamous epithelium and are most commonly found in the cervical esophagus. Webs are usually detected incidentally during barium x-rays and rarely occlude enough of the esophageal lumen to cause dysphagia. The etiology of these webs is unclear. Most are probably congenital in origin. In some instances postcricoid esophageal webs are associated with iron deficiency and dysphagia – the so-called *Plummer-Vinson* or *Paterson-Kelly* syndrome. This syndrome is associated with increased risk of hypopharyngeal cancer and should be managed with bougienage, iron replacement and careful follow-up. Esophageal webs may also form after esophageal injury, such as that induced by pills or lye ingestion, and have also been reported in association with graft-versus-host disease. The lower esophageal or *Schatzki's ring* is also a membrane-like structure, but unlike webs is lined by squamous epithelium on its superior aspect and columnar epithelium inferiorly. Such a ring is quite common, being detected in up to 10% of all upper GI barium x-rays. Few produce sufficient luminal obstruction to cause dysphagia (yet a lower esophageal ring is a common cause of dysphagia). When the lumen is narrowed to a diameter of 13 mm or less, the patient will experience intermittent solid-food dysphagia or even episodic food-bolus obstruction. Treatment of a symptomatic Schatzki's ring involves shattering the ring with a large-diameter bougie or a balloon dilator. Subsequent

treatment with a proton pump inhibitor has been shown to decrease the recurrence of symptomatic Schatzki's rings.

13.2. Diverticula

Pharyngoesophageal diverticula are outpouchings of one or more layers of the pharyngeal or esophageal wall and are classified according to their location.

13.2.1. Zenker's Diverticulum (Figure 18)

This diverticulum arises posteriorly in the midline between the oblique and transverse (cricopharyngeal) fibers of the inferior pharyngeal constrictor muscles. As this diverticulum enlarges, it usually shifts to the left of the midline. Zenker's diverticulum forms because of decreased compliance of the cricopharyngeal muscle, which results in abnormally high pressures in the hypopharynx during deglutition. In addition to pharyngeal-type dysphagia, Zenker's diverticulum may be associated with effortless regurgitation of stagnant, foul-tasting food, as well as aspiration. A very large diverticulum can produce a neck mass, usually on the left side.

Treatment of a symptomatic Zenker's diverticulum is surgical. Most surgeons will either resect the diverticulum or suspend it (diverticulopexy) so that it cannot fill. This is combined with cricopharyngeal myotomy. In many cases, particularly if the diverticulum is small, cricopharyngeal myotomy alone will alleviate symptoms. This procedure can now be performed endoscopically in selected cases. Once the cricopharyngeal myotomy has been performed, the patient has lost an important defense mechanism to prevent the aspiration of refluxed material.

Figure 18. Lateral barium x-ray of a Zenker's diverticulum (white arrow). These diverticuli form just above the poorly relaxing cricopharyngeus muscle, which appears as a cricopharyngeal "bar" (black arrow). These diverticuli extend posteriorly and.most tend to shift to the left of the midline as they enlarge.

The patient should therefore be instructed to elevate the head of the bed in order to minimize this risk. For the same reason patients with severe GERD should not undergo cricopharyngeal myotomy unless the reflux can be controlled either medically or surgically.

13.2.2. Midesophageal Diverticula

Traditionally, midesophageal diverticula have been called "traction" diverticula because of their supposed etiology. They were believed to arise secondary to old mediastinal inflammation, such as tuberculosis, that caused adherence of mediastinal structures to the outer esophageal wall so that outward traction occurred during peristalsis. It now appears likely that very few midesophageal diverticula arise this way. In most there is an associated motility disorder and it is likely that this is actually a "pulsion" diverticulum formed when a peristaltic wave deteriorates into a simultaneous or spastic contraction in the smooth-muscle esophagus. Midesophageal diverticula rarely require specific therapy. Rather, the associated motor disorder requires treatment if symptomatic.

13.2.3. Lower Esophageal or Epiphrenic Diverticula

These "pulsion" diverticula form just above the LES and are invariably associated with an esophageal motor disorder – usually diffuse esophageal spasm, with or without abnormal relaxation of the LES. Patients with these diverticula usually present with dysphagia and/or angina-like chest pain. In addition, they may complain of nocturnal regurgitation of large quantities of stagnant fluid. If symptoms are present, treatment with nitrates or calcium channel blockers may be helpful. If this is not successful, surgery is indicated. Any surgical attack on these diverticula should involve a myotomy of the spastic distal esophagus and/or LES. Resection of the diverticula alone seldom affords long-term benefit.

13.2.4. Intramural Diverticulosis

This disorder has a characteristic radiologic appearance consisting of numerous tiny, flask-shaped outpouchings from the esophageal lumen. There is usually an associated smooth stricture in the proximal esophagus. Patients typically present with dysphagia that responds to peroral dilation. The outpouchings are actually dilated ducts coming from submucosal glands and thus are not true diverticula. The etiology is obscure. Some cases are associated with esophageal candidiasis, but this organism does not appear to be of etiological importance.

13.3. Esophageal Trauma

Blunt or penetrating trauma to the chest can cause esophageal injury. In addition, esophageal instrumentation such as that used in bougienage, endoscopy or stent insertion may cause perforation or mucosal laceration. Severe retching or vomiting can also cause esophageal perforation (*Boerhaave's syndrome*) or mucosal laceration (*Mallory-Weiss tear*). Boerhaave's syndrome is a life-threatening condition that requires immediate surgery to drain the mediastinum and repair the defect in the esophageal wall. Patients, typically alcoholics, present with sudden epigastric and/or chest pain following a bout of vomiting and usually have fever and signs of hypovolemia or shock. The diagnosis is established by having the patient swallow a small amount of water-soluble contrast material (e.g., Gastrografin®), which is seen to leak into the mediastinum or pleural cavity through the esophageal perforation. CT of the chest may also reveal an esophageal perforation. If the perforation is large, a chest x-ray may be diagnostic.
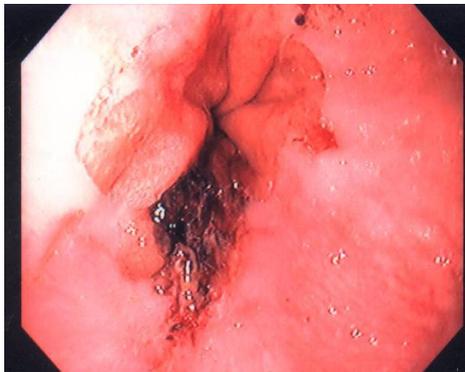
The mucosal laceration of the 'Mallory-Weiss' tear (Figure 19) is probably better classified as a disorder of the stomach, because in most cases the laceration starts at the GE junction and extends down into the stomach. These patients present with hematemesis or melena following a bout of retching or vomiting. The bleeding usually stops spontaneously and only supportive therapy is required. If bleeding persists, endoscopically applied hemostasis or surgical intervention may be necessary.

Figure 19. Endoscopic view of a Mallory-Weiss tear. Note the mucosal laceration with blood clot at its base at the gastroesophageal junction. Patients with this lesion typical have vigorous retching or vomiting before vomiting up fresh blood and/or passing melena.

13.4. Food-Bolus Obstruction and Foreign Bodies

A surprising variety of foreign bodies can lodge in the esophagus after being swallowed either inadvertently or deliberately. The three most common sites where foreign bodies become stuck are the piriform sinuses, at the aortic arch and just above the LES. The patient can usually localize the site of the obstruction quite accurately, and this can be confirmed using routine x-rays if the object is radiopaque. Most foreign bodies can be removed by an expert endoscopist. Surgery is rarely required, except when perforation has occurred. A more common clinical problem is esophageal food-bolus obstruction. This typically occurs when a patient with a motility disorder, esophagitis, stricture or Schatzki's (lower esophageal) ring swallows a large solid-food bolus. The patient notices immediate pain, usually well localized to the site of obstruction in the chest, but sometimes referred to the suprasternal notch. Attempts to swallow anything further are unsuccessful and usually lead to prompt regurgitation. Many physicians will initially treat these patients with smooth-muscle relaxants such as intravenous glucagon or sublingual nitroglycerin; however, there is little evidence that this approach is efficacious. Drinking carbonated beverages may also help the bolus pass, presumably by distending the esophageal lumen with gas. If the food bolus does not pass on spontaneously within a few hours, endoscopy should be performed, at which time the bolus can either be removed per os or pushed through into the stomach. A persistent food bolus impaction, if left untreated for a long period (> 12-24 hours), may lead to mucosal ulceration and even a localized perforation.

Chapter 3: Scientific Basis of Gastric Disorders

A.B.R. Thomson and R.H. Hunt

1. Introduction

Diseases of the GI tract are common, accounting for about one out of seven persons presenting to their primary care physician. Disorders of the stomach and duodenum make up a large part of these.

It has been known for many centuries that the gastric juice is acidic in nature, but it was not until 1824 that William Prout established that the acid in the stomach is hydrochloric acid. Since then physicians have been fascinated by the ability of the healthy stomach and duodenum to withstand hydrochloric acid and pepsin. In particular, the mechanisms controlling gastric secretion have been extensively studied in the hope of finding a satisfactory way to explain and treat peptic ulcer disease. Further studies turned to the role of mucus, bicarbonate and prostaglandins in the maintenance and defence of the gastric mucosa against acid injury. In 1983 Marshall and Warren isolated the bacteria now known as *Helicobacter pylori* (Figure 1) from gastric biopsies in duodenal ulcer patients. They won the Nobel Prize in Medicine, and a new era in the understanding and treatment of gastroduodenal disease was born. This chapter will review the anatomy, clinical physiology and related common disorders of the stomach and duodenum.

2. Anatomy

The stomach is the most capacious part of the GI tract and lies between the distal esophagus and the duodenum. It is situated entirely within the abdomen below the diaphragm (Figure 2). The body of the stomach lies slightly to the left of the midline; the antrum crosses the spinal vertebrae at the level of T10-L1, and the pylorus lies to the right of the vertebral column. The duodenum is predominately retroperitoneal and comprises the cap, the descending and the distal portions.
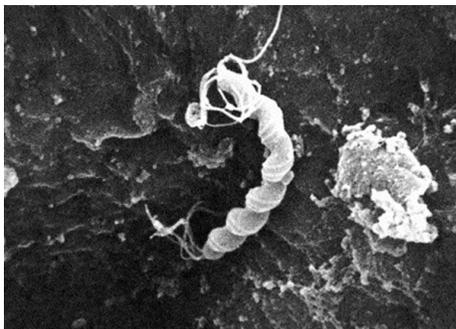

Figure 1. *Helicobacter pylori*. (Courtesy of McMaster University Medical Centre Electron Microscopy Lab.)

The greater curvature is some three or four times the length of the lesser curvature. A point known as the angulus or incisura may be defined on the lesser curvature. This point is relatively constant and marks a change from the prominent rugal folds of the gastric body to the smoother, less-prominent folds of the antrum.

The stomach and duodenum lie in close proximity to a number of impor- tant anatomic structures. Anterosuperiorly are the left diaphragm and left lobe of the liver, while the body and tail of the pancreas lie posteriorly. Laterally to the left are: the hilum of the left kidney, the left adrenal gland and, above that, the spleen. These organs form the stomach bed and are separated from it by the lesser omentum and the lesser sac.
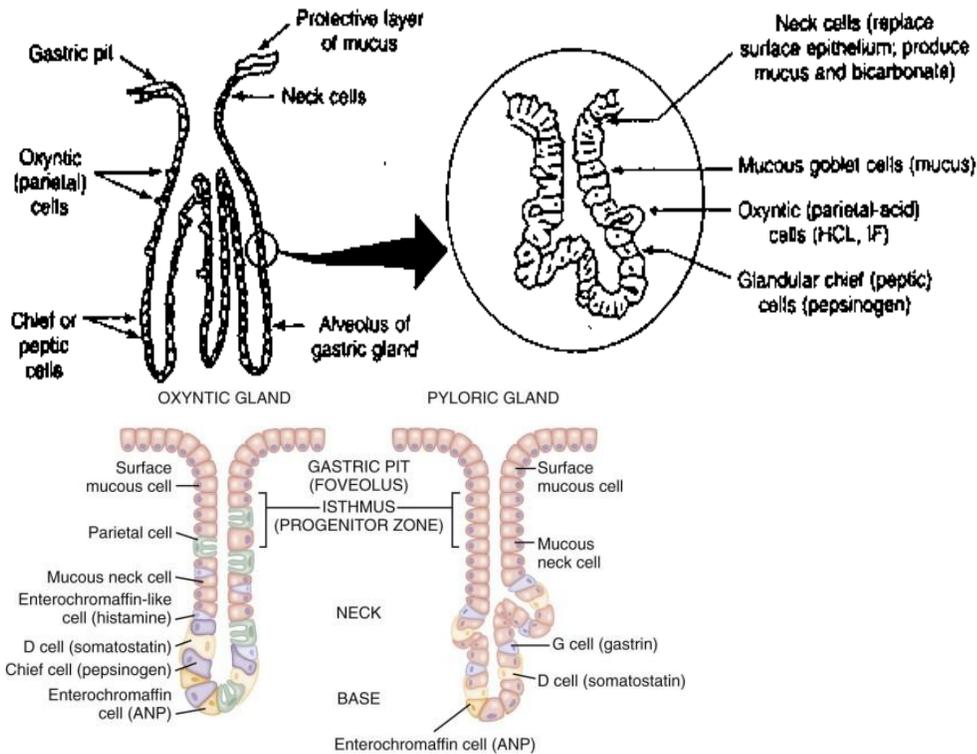
Figure 2. Microscopic appearances of gastric pit and glands.
   o Somatostatin-containing D cells contain cytoplasmic processes that terminate in the vicinity of acid-secreting parietal and histamine-secreting enterochromaffin-like cells in the oxyntic gland area (fundus and corpus) and gastrin-secreting G cells in the pyloric gland area (antrum).
   o The functional correlate of this anatomic coupling is a tonic paracrine restraint on acid secretion by somatostatin that is exerted directly on the parietal cell as well as indirectly by inhibiting histamine and gastrin secretion. ANP, atrial natriuretic peptide.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-4, pg 819, Ninth Edition, 2010

Vagal reflexes initiated during the initial phase of eating, the lower luminal acidity and distention caused by the entrance of food into the stomach stimulate release of hormones by the enteroendocrine cells of the stomach. Gastrin (from G cells) is released into the bloodstream and is carried by the blood to the mucosa of the stomach where it stimulates HCl production. Enterochromaffin-like (ECL) cells are stimulated by gastrin to release histamine, and it is thought that the stimulation of parietal cells is mainly due to histamine binding secondary to gastrin's effects on histamine release. Protein in food is also a potent stimulator of gastrin release.
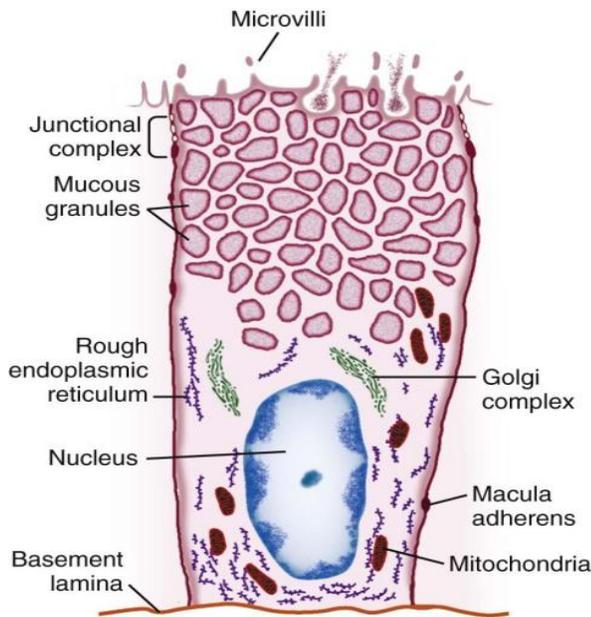
Figure 3. Schematic representation of a surface mucous cell.
Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 47-4, pg 776, Ninth Edition, 2010

The sympathetic nerve supply arises from the spinal cord between T6 and T10 and passes to the sympathetic ganglia. The parasympathetic supply con- tracts the stomach, relaxes the pylorus and stimulates acid, pepsin and mucus secretion, whereas sympathetic stimulation constricts the blood supply and reduces gastric motor activity and secretion while the pylorus is contracted.

3. Functions of the Stomach

The food bolus exits the lower esophageal sphincter through the cardiac orifice, the opening that connects the cardia region of the stomach to the esophagus. Vagal reflexes initiated by the cephalic phase of eating inhibit contractile activity in the proximal stomach and the entry of food into the stomach promotes relaxation of the cardia of the stomach. Upon entry of food into the stomach, the stomach muscles relax. When relaxed and empty, the adult human stomach has a near empty volume, but it normally expands to hold about 1 L of food and liquid. The stomach temporarily stores the swallowed food and liquid until it is passed to the intestines. The stomach secretes HCl and for initiating digestion, intrinsic factor which is essential for vitamin B_{12} absorption in the small intestine, and also secretes endocrine hormones. Ghrelin is another hormone released by the stomach. The release of ghrelin is stimulated by fasting and is suppressed by the ingestion of food. Ghrelin stimulates gastric emptying and acts via the central nervous system to stimulate appetite. The stomach mixes up food and digestive juice and macerates the mixture into a semiliquid state, called chyme. Gastric inflammatory mediators can modulate gastric secretion and motility. Finally, the stomach regulates the rate of entry of chyme into the duodenum.

Table 1. Functions of the Stomach

> Storage reservoir
> Secretion of HCl, digestive enzymes and peptides
> Mixing of food with gastric juice
> Controlled release of food/fluid into duodenum
> Contributes to regulation of food intake
> Immune modulation.

3.1. Acid Secretion

The thick layers of gastric mucosa secrete gastric juice, which contains two key substances involved in digestion: hydrochloric acid and pepsin. Gastric juice also contains mucus, bicarbonate, water, and minerals- all involved in protecting the gastric mucosa from the destructive forces of acid and pepsin and also intrinsic factor, required for the absorption of vitamin B_{12}.

Parietal cells contain secretory channels called canaliculi from which the gastric acid is secreted into the lumen of the stomach. Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi. H^+ ions are generated within the parietal cell from dissociation of H_2O. The OH^- ions formed in this process combine with CO_2 , in a reaction catalyzed by carbonic anhydrase, to form HCO_3^-. The HCO_3^- is transported out of the cell in exchange for Cl^- ions. Thus the parietal cell now has a supply of both H^+ and Cl^- ions for secretion. Cl- and K^+ ions are transported into the lumen of the cannaliculus by conductance channels.

- In the resting state, H^+,K^+-ATPase is sequestered within cytoplasmic tubulovesicles and is inactive.
- On stimulation, the tubulovesicles move to and fuse with the apical membrane, forming an extensive canalicular system.
- Translocation of H^+,K^+-ATPase into the canalicular membrane together with the presence of luminal K^+ activates the enzyme.
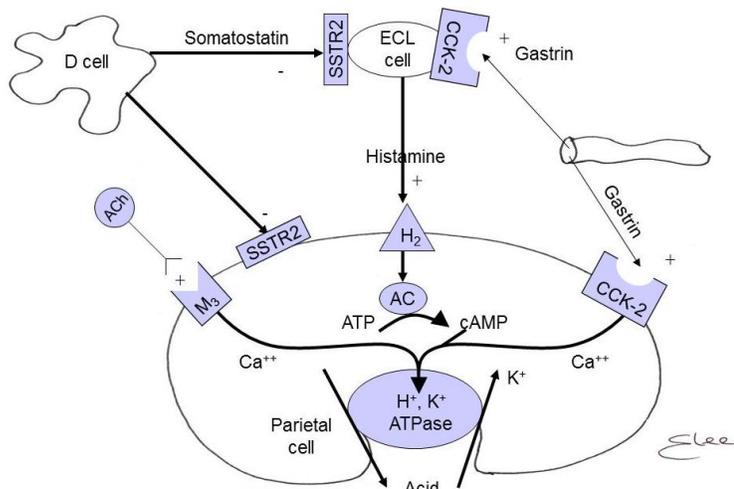
Figure 4. Model illustrating parietal cell receptors and transduction pathways.

- The principal stimulants of acid secretion at the level of the parietal cell are histamine (paracrine), gastrin (hormonal), and acetylcholine (ACh; neurocrine).
- Histamine, released from enterochromaffin-like (ECL) cells, binds to H_2 receptors that activate adenylate cyclase (AC) and generate adenosine 3′,5′-cyclic monophosphate (cAMP).
- Gastrin, released from G cells, binds to cholecystokinin-2 (CCK-2) receptors that activate phospholipase C (not shown) to induce release of cytosolic calcium (Ca^{++}).

- o Gastrin stimulates the parietal cell directly and, more importantly, indirectly by releasing histamine from ECL cells.
- o ACh, released from intramural neurons, binds to M_3 receptors that are coupled to an increase in intracellular calcium.
- o The intracellular cAMP- and calcium-dependent signaling systems activate downstream protein kinases, ultimately leading to fusion and activation of H^+,K^+-ATPase, the proton pump.
- o Somatostatin, released from oxyntic D cells, is the principal inhibitor of acid secretion.
- o Somatostatin, acting via the SSTR2 receptor, inhibits the parietal cell directly as well as indirectly by inhibiting histamine release from ECL cells. +, stimulatory; −, inhibitory.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-10, pg 777 and 821, Ninth Edition, 2010.

- o Efferent vagal fibers synapse with intramural gastric cholinergic (ACh) and peptidergic (gastrin-releasing peptide [GRP] and vasoactive intestinal peptide [VIP]) neurons. In the fundus (oxyntic mucosa), ACh neurons stimulate acid secretion directly as well as indirectly by inhibiting somatostatin (SST) secretion, thus eliminating its restraint on parietal cells and histamine-containing enterochromaffin-like (ECL) cells.
- o In the antrum (pyloric mucosa), ACh neurons stimulate gastrin secretion directly as well as indirectly by inhibiting SST secretion, thus eliminating its restraint on gastrin-containing G cells. GRP neurons, activated by luminal protein, also stimulate gastrin secretion.
- o VIP neurons, activated by low-grade gastric distention, stimulate SST and thus inhibit gastrin secretion.
- o Dual paracrine pathways link SST-containing D cells to parietal cells and to ECL cells in the fundus.
- o Histamine released from ECL cells acts via H_3 receptors to inhibit SST secretion.
- o This serves to accentuate the decrease in SST secretion induced by cholinergic stimuli and thus augments acid secretion. In the antrum, dual paracrine pathways link SST-containing D cells to gastrin cells.
- o Release of acid into the lumen of the stomach restores SST secretion in both the fundus and antrum; the latter is mediated via release of calcitonin gene-related peptide (CGRP) from extrinsic sensory neurons.
- o Acute infection with *Helicobacter pylori* (HP) also activates CGRP neurons to stimulate SST and thus inhibit gastrin secretion.
- o In duodenal ulcer patients who are chronically infected with HP, the organism or cytokines released from the inflammatory infiltrate inhibit SST and thus stimulate gastrin (and acid) secretion.
- o Acid secretion requires a functional H^+,K^+-ATPase as well as apical K^+ and Cl^- channels and basolateral transporters and/or channels for K^+, Cl^-, and HCO_3^-.
- o Acid is produced from the hydration of CO_2 to form H^+ and HCO_3^-, a reaction catalyzed by cytoplasmic carbonic anhydrase (CA).
- o In the presence of luminal K^+, H^+,K^+-ATPase pumps H^+ into the lumen in exchange for K^+.

- o Luminal K^+ channels (KCNE2/KCNQ1 and ROMK [not shown]) recycle K^+ across the luminal membrane.
- o The source of intracellular K^+ is the basolateral Na^+,K^+-ATPase and the sodium-2 chloride potassium-cotransporter-1 (NKCC1).
- o For each H^+ secreted, a HCO_3^- exits the cell across the basolateral membrane via the anion exchanger (AE2, or Slc4a2).
- o Concurrently with H^+, Cl^- is extruded across the luminal membrane via an apical chloride channel. The sources of intracellular Cl^- are AE2, NKCCl, and the SLC26A7 channel.
- o SST-containing D cells are structurally and functionally coupled to their target cells: parietal, enterochromaffin-like (ECL), and gastrin cells.
- o SST, acting via SSTR2 receptors, tonically restrains acid secretion.
- o This restraint is exerted directly on the parietal cell as well as indirectly by inhibiting histamine secretion from ECL cells and gastrin secretion from G cells.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-5, pg 820 and 824, Ninth Edition, 2010

3.2 Motility
- o Slow waves originate in the pacemaker region located at the juncture of the fundus and the corpus on the greater curvature.
- o Note the fundus does not have slow wave activity (electrode A).
- o Slow waves propagate circumferentially and migrate distally to the pylorus approximately every 20 seconds, or 3 cycles per minute (cpm*) (dotted lines with arrowheads).*
- o The myoelectrical activity of the slow wave can be recorded with cutaneous electrodes.
- o The summed gastric myoelectrical activity recorded from electrodes positioned on the abdominal surface in the epigastrium is termed an electrogastrogram (EGG), and the normal rhythm is 3cpm.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 48-1, pg 790 and 791, Ninth Edition, 2010

- o The plateau and action potentials occur during circular muscle contractions. Peristaltic waves originate in the pacemaker area. The frequency (3 cycles per minute [cpm]) and propagation velocity (approximately 14 mm/second) of the gastric peristaltic waves are controlled by the slow wave, which leads the contraction from the proximal corpus to the distal antrum, as shown at electrodes A through D.
- o The *solid black lines* and *arrows* indicate the circumferential and distal propagation of the peristaltic wave, which forms a ring contraction (*small arrow*), indicating a moving peristaltic contraction. Peristaltic contractions occur three times per minute, the frequency of the gastric slow wave.
- o The increased myoelectrical activity of the plateau potentials and action potentials linked with the slow wave results in increased amplitude of the EGG signal *(thick black lines)*.
- o The fundus does not participate in the gastric peristaltic contractions.

Gastric Emptying
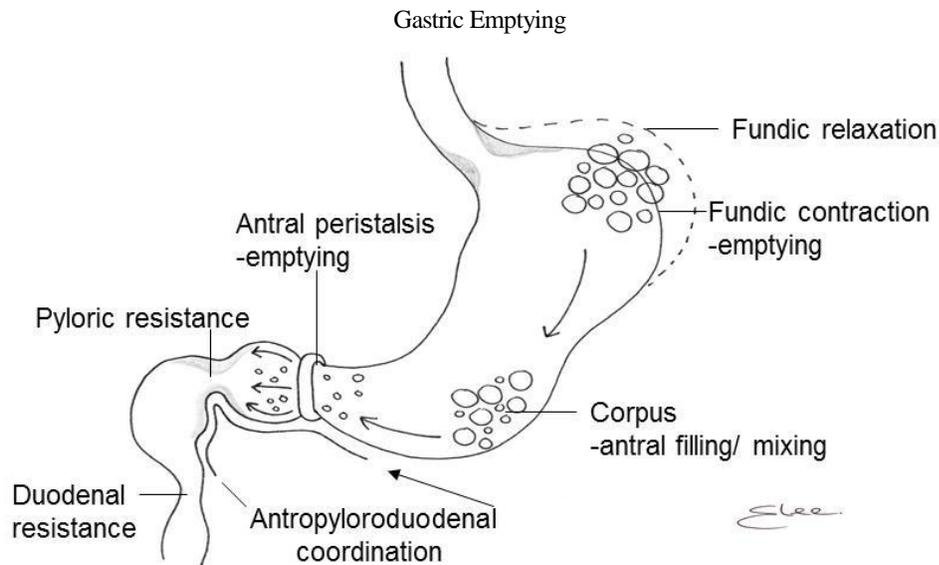
Figure 5.
- The fundus then contracts to empty the ingested food into the corpus and antrum for trituration and emptying.
- Recurrent corpus-antral peristaltic waves mill the solids into chyme, which is composed of 1- to 2-mm solid particles suspended in gastric juice.
- Antral peristaltic waves, indicated by the ring-like indentation in the antrum, empty 2 to 4 mL of the chyme through the pylorus and into the duodenal bulb at the slow wave frequency of three peristaltic contractions per minute.
- Antropyloroduodenal coordination indicates efficient emptying of chyme through the pylorus, which modulates flow of the chyme by varying sphincter resistance.
  Contractions in the duodenum also provide resistance to emptying.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 48-8, pg 795, Ninth Edition, 2010

Neural connections between the stomach and CNS
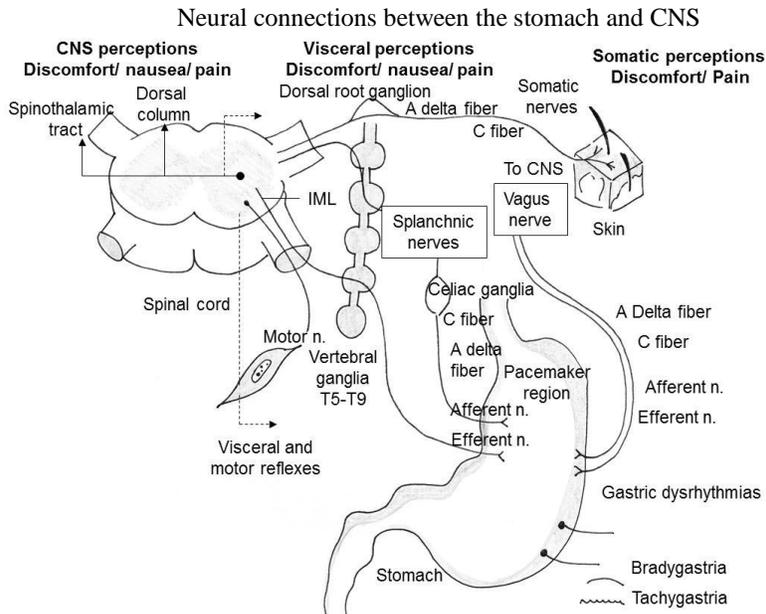
Figure 6

- o The vagus nerve contains afferent nerves with A-delta and C pain fibers with cell bodies in the nodose ganglia with connections to the nucleus tractus solitarius (not shown).
- o Low threshold mechano- and chemoreceptors stimulate visceral sensations such as stomach emptiness or fullness and symptoms such as nausea and discomfort.
- o These stimuli are mediated through vagal pathways and become conscious perceptions of visceral sensations if sensory inputs reach the cortex.
- o The splanchnic nerves also contain afferent nerves with A-delta and C fibers that synapse in the celiac ganglia with some cells bodies in the vertebral ganglia (T5-T9)
- o Interneurons in the white rami in the dorsal horn of the spinal cord cross to the dorsal columns and spinothalamic tracts and ascend to sensory areas of the medulla oblongata..
- o These splanchnic afferent fibers are thought to mediate high-threshold stimuli for visceral pain. In contrast to visceral sensations, somatic nerves such as from the skin carry sensory information via A-delta and C fibers through the dorsal root ganglia and into the dorsal horn and then through dorsal columns and spinothalamic tracts to cortical areas of somatic representation.
- o Changes in gastric electrical rhythm, excess amplitude contractions, or stretch on the gastric wall are peripheral mechanisms that elicit changes in afferent neural activity (via vagal and/or splanchnic nerves) that may reach consciousness to be perceived as visceral perceptions (symptoms) emanating from the stomach. IML, intermediolateral nucleus; n., nerve.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 48-17, pg 801, Ninth Edition, 2010.

Table 2. Mechanism of action of prokinetic drugs used for the treatment of symptoms of gastroparesis, as well as nausea and vomiting arising from dysmotility of the GI tract. The FDA pregnancy category is shown in brackets

Drug	Receptor
➤ Metoclopramide (B)	○ Central/peripheral dopamine receptor antagonist (D_2)
	○ 5-HT3 receptor antagonist
	○ 5-HT4 receptor agonist
➤ Domperidone (C)	○ peripheral D_2 antagonist
➤ - Cisapride (C)	○ muscarinic (acetylcholine) receptor agonist
	○ 5-HT3 receptor antagonist
	○ 5-HT4 receptor agonist
➤ - Ondansatron (B)	○ 5-HT3 receptor antagonist
➤ - Erythromycin (B)	○ motilin receptor agonist
➤ - Tegaserod	○ Cholinergic 5-HT4 partial agonist
➤ - Bethanechol	○ muscarinic receptor agonist
➤ Anticholinergic (buscopan, for tachygastria)	
➤ - α-adrenergic antagonists	○ α-adrenergic antagonist
➤ - Botulism toxin injection	○ phosphodiesterase inhibitirs (Viagra®)
➤ - Octreotide injection	○ somatostatin receptor agonist

Adapted from: Quigley EMM. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 1007.

Dumping syndrome is a frequent compilation of esophageal, gastric or bariatric surgery. The early postprandial phase results from the rapid emptying of the stomach including larger than normal food particles, with the osmotic shift of fluid into the duodenal lumen plus the distention of the human releasing gastrointestinal and pancreatic hormones. These hormones cause the gastrointestinal and vascular symptoms of the early dumping syndrome. The rapid and early absorption of nutrients causes prompt secretion of insulin, and the late dumping syndrome characterized by reactive hypoglycaemia (Tack et al. 2009). A modified oral glucose tolerance test may be used to establish the reactive hypoglycaemia. The dumping syndrome does not always respond to dietary maneuvers, and pectin or guar gum may be needed to slow gastric emptying, a carbose to slow starch digestion and reduce pos-prandial reactive hypoglycaemia, or in extreme cases somatostatin injections may be given to slow gastric emptying and to slow sugar absorption.

There are many causes of nausea and vomiting, some due to disorders of the GI tract and some due to disorders affecting the central vomiting centre. The vomiting centre is on the blood side of the blood-brain barrier. There are numerous centrally acting drugs used for the treatment

of the symptoms of nausea and vomiting (Table 3). Some persons with severe, intractable gastroparesis, such as may occur with severe type I diabetes, may improve with near-total gastrectomy and Roux-en-Y anastomosis. Slowed gastric emptying and delayed small intestinal transit occur in persons with cirrhosis. If these symptoms are due to disorders of the upper GI tract, then stimulating smooth muscle activity is useful, as outlined in Table 2. If intractable symptoms persist, acupuncture (P6 point) or gastric electrical stimulation may be of limited benefit. Unfortunately, nausea and vomiting is common during pregnancy, particularily during the first trimester. Curiosly, vitamin b6 (thiamine), soda crackers, and ginger are often helpful (Table 4). If symptoms persist, there are a number of medications which can safely be used during pregnancy, especially FDA category A and B (Table 5).

Table 3. Mechanisms of centrally acting drugs used for the treatment of symptoms of nausea and vomiting

H-1 receptor antagonists – diphenohydramine, promethazine

Cannabinoids – dronabinol, nabilone

Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant

Neuroleptic – chlorpromazine, haloperidol

Benzodiazepines

5 HT3 antagonist - Ondansatron

Tricylic antidepressants

Steroids (e.g. dexamethasone) (Mannitol (nausea and vomiting due to increased intracranial pressure)

Table 4. Non-pharmaceutical options (Dietary and lifestyle modifications) for the treatment of nausea and vomiting during pregnancy

Avoidance of precipitating factors

Frequent, small meals high in carbohydrate and low in fat

Vitamin B6 (thiamine)

Ginger

Stimulation of P6 acupuncture point

Treat dehydration, electrolyte disturbances

Correct malnutrition

Soda crackers (unproven benefit)

Avoid offending foods/beverages

Modified from: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 433.

Table 5. Drugs that may be used for nausea and vomiting in pregnancy and their FDA pregnancy use category

Drug	FDA category	Usual dosage
Vitamin B_6	A	10-25 mg three times daily
Doxylamine	B	12.5 mg twice daily
Erythromycin	Erythromycin (FDA category B; used rarely to treat hyperemesis)	Erythromycin (FDA category B; used rarely to treat hyperemesis)
Prochlorperazine	C	5-10 mg three times daily
Metoclopramide	B	10-20 mg four times daily
Ondansetron	B	4-8 mg three times daily
Promethazine	C	12.5-25.0 mg four times daily
Domperidone	C	20 mg three to four times daily

Adapted from: Thukral C, and Wolf JL. *Nature Clinical Practice Gastroenterology & Hepatology* 2006; 3(5): page 258; and printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 433.

Table 6. Smooth muscle as well as the CNS receptors responsible for the mechanism (s) of action for drugs used in the treatment of refractory nausea and vomiting

➢ GI receptors
➢ Central
   o H-1 receptor antagonists – diphenohydramine, promethazine
   o Cannabinoids – dronabinol, nabilone
   o Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant
   o Neuroleptic – chlorpromazine, haloperidol
   o Benzodiazepines
   o Ondansatron – 5 HT3 antagonist
   o Tricylic antidepressants
   o Steroids (e.g. dexamethasone), mannitol (nausea and vomiting due to increased intracranial pressure)

Table 7. Factors that slow the rate of gastric emptying rate

➢ Gastric Neuromuscular
   o Tachygastria
   o Decreased fundic accommodation
   o Increased fundic accommodation
   o Antral hypomotility
   o Pylorospasm
   o Antroduodenal dyscoordination

- Meal-related factors
  - Increased acidity
  - Increased osmolarity
  - Nutrient density: fat > protein > CHO
  - Tryptophan
  - Undigestible fibers
- Small intestinal factors
  - Fatty acids in duodenum
  - Fatty acids in ileum
- Colonic factors
    Constipation, IBS
- Other factors
  - Hyperglycemia
  - Hypoglycemia
  - Illusory self-motion (vection)

Abbreviations : CHO, carbohydrate; IBS, irritable bowel syndrome.

Only ↓ fundic accommodation and hypoglycemia accelerate gastric emptying. The volume of the meal alters the rate of gastric emptying in proportion to the volume of the meal.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 48-1, pg   , Ninth Edition, 2010

4. Hypergastrinemia
      From our appreciation of the numerous ways in which acid secretion may be turned on or off, it is straight-forward to work out the causes of hypergastrinemia, and those mechanisms of hypergastrinemia which would be associated with increased gastric acid secretion, and might lead to severe peptic ulcer disease (Table 8 and 9)

Table 8. Causes of hypergastrinemia

With acid hypersecretion	With variable acid secretion	With acid hyposecretion
Gastrinoma	Hyperthyroidism	Atrophic gastritis
Isolated retained gastric antrum	Chronic renal failure	Pernicious anemia
Antral G-cell hyperplasia	Pheochromocytoma	Gastric cancer
Massive small bowel resection		Postvagotomy and pyloroplasty
Pyloric outlet obstruction		
Hyperparathyroidism		

Table 9. Mechanisms of hypergastrinemia associated with gastric acid (HCl), hypersecretion and with HCl hyposecretion or achlorydria.

- ➤ ↑ Stimulation
  - o Non-fasting
  - o Gastric outlet obstruction
  - o Hyperthyroidism
  - o Pheochromocytonon
  - o Hypercalcemin
  - o Mastocytosis

- ➤ ↓ Metabolism
  - o Chronic renal failure

- ➤ ↓ Feedback inhibition
  - o Atropic gastritis (pernicious anemia, Hp infection, gastric cancer)
  - o Reduced acid – PPI, H_2RA, antacids
  - o Retained antrum

- ➤ ↑ Secretion
  - o ZES, MEN-1˚, G-cell
  - o Hypertrophy/hyperplasia
  - o Retained gastric antrum

Adapted from: Metz DC, and Jensen RT. *Gastroenterology* 2008;135: page 1469-1492.

While peptic ulcer disease (PUD) is usually caused by *H. pylori* infection or NSAIDs, in many non-explanation is found (idiopathic). A very uncommon cause of PUD is hypergastrinemia, associated with a gastrin producing tumor. The normal control of gastrin secretion is lost, and the hypergastrinemia may cause numerous symptoms (Table 10) as part of the Zollinger-Ellison syndrome (ZES). For persons with PUD as part of their ZES, they often have a history of multiple ulcers, ulcers at usual sites, ilcers which are slow to heal, or are complicated.

Table 10. Presenting features of ZES, and their approximate frequency

o Abdominal pain (75%-100%)	o Multiple ulcers in unusual places
o Diarrhea (35%--73%) (isolated presentation in up to 35%)	o Stomal ulcers
	o PUD refractory to treatment
o Pain and diarrhea (55%-60%)	o Ulcer complications (bleeding, 1%-17%; perforation, 0%-5%, or obstruction, 0%-5%)
o Heartburn (44%-64%)	
o Duodenal and prepyloric ulcers (71%-91%)	o Associated with MEN1 (22%-24%)

Abbreviations: MEN, multiple endocrine neoplasia; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

Adapted from: Metz DC, and Jensen RT. *Gastroenterology* 2008;135: page 1469.

In the person suspected as having ZES (Table 10), a fasting gastrin measurement is obtained. There are many possible explanations for an elevated serum gastrin concentration (Table 9). After these have been considered and exluded, if there is a high pretest probability of ZES, then proceed with diagnostic investigations (Table 11). There are mostly parathyroid, pancreatic and pituitary tumours associated with MEN-1 (Table 12). For MEN-1 associated with a gastrinema and ZES, management is usually PPI acid inhibition, and resection or

chemotherapy if the tumour is suspect of being malignant. Treatment is complex and requires specialist consultation.

Table 11. Investigation of the patient with confirmed fasting hypergastrinemia, performed after a detailed history and physical examination

- ➢ Laboratory tests
  - o Confirm fasting state for gastrin measurement
  - o Creatinine, calcium, PTH
  - o Chromogranin A (exclude renal failure)
  - o Schillings test, serum B_{12}

- ➢ Provocative tests
  - o Secretin infusion (increases gastrin paradoxically in ZES)
  - o TSH
  - o Urinary metanephrins
  - o Ca^{+2} infusion (marked increase in serum gastrin)
  - o Basal and pentagastrin stimulated acid secretion (↑↑ BAO), BAO/MAO>60% (ZES)
  - o Food-stimulated acid secretin (G-cell hyperplasia/ hyperfunction)

- ➢ Endoscopy
  - o EGD
    - Multiple ulcers in unusual sites
    - Biopsy antrum for G-cell number (to distinguish between G-cell hyperplasia [↑G-cell number] vs G-cell hyperfunction (normal G-cell number); *H. pylori*
    - Thick gastric folds
    - EUS for possible tumor localization

- ➢ Diagnostic imaging
  - o Abdominal ultrasound
  - o CT/ MRI, head (pituitary fossa, tumor in MEN I)
  - o Ostreotide scan
  - o MBIG scan
  - o CT scan of abdomen
  - o MRI of abdomen
  - o Parathyroid scan

Abbreviations: EUS, endoscopic ultrasound; ZES, Zollinger-Ellison syndrome

Table 12. Tumors found in patients with multiple endocrine neoplasia-type I (MEN-1)
(their approximate frequency % is shown for interest.)

Tumors

- ➢ Parathyroid (90)

- ➢ Pancreas (80)
  - o Gastrinoma (50)
  - o Insulinoma (20)
  - o Glucagonoma
  - o VIPoma

- ➢ Pituitary (40)
  - o Prolactin-secreting (30)
  - o Growth-hormone secreting (15)
  - o Cushing's syndrome (15)

- ➢ Adrenal cortical adenoma (20)

- ➢ Thyroid adenoma (20)

Chapter 4: Dyspepsia, Peptic Ulcer Disease and Upper GI Bleeding

A.B.R. Thomson and R.H. Hunt

1. Dyspepsia

"Dyspepsia" is defined as pain or discomfort in the upper abdomen. It is one of the most common complaints bringing patients to consult their family physician. These patients may also complain of nausea, fullness, early satiety, bloating, or regurgitation. Dyspepsia is a symptom or symptoms, and when the person presents, their symptom is not diagnosed, so this is called uninvestigated dyspepsia.

Each year, dyspepsia occurs in about 25% of the North American population. 25% of patients with chronic dyspepsia have esophagitis due to gastroesophageal reflux disease (GERD), 5-10% have peptic ulcer disease (PUD), < 2% have gastric or esophageal cancer, and the rest have a normal endoscopy (functional or idiopathic dyspepsia).

Lifestyle factors such as smoking, excess alcohol intake, stress and a high fat diet could precipitate dyspeptic symptoms. Non-ulcer dyspepsia (NUD) and non-erosive reflux disease (NERD) are types of functional dyspepsia with PUD-like and GERD-like symptoms respectively (Figure 1). Unlike PUD and GERD, NUD and NERD are not associated with erosive mucosal findings when investigated by esophagogastroduodenoscopy (EGD). The severity of dyspeptic symptoms is not useful in predicting what the result of the EGD might be, and there is no relationship between the severity of symptoms and the severity of underlying pathology of esophagitis or PUD.

Table 1. Commonly Used Terms to be Distinguished

➢	Dyspepsia	- A symptoms or symptoms, with no known diagnosis because the symptom has not be investigated. (aka undiagnosed dyspepsia)
➢	FD	- Functional dyspepsia: dyspepsia in which EGD and possibly other tests as well are normal
➢	NERD	- Normal endoscopy reflux disease: because GERD is a cause of dyspepsia, and GERD symptoms are included in the definition, this term may be used in the person with dyspepsia and a normal EGD
➢	NUD	- Non-ulcer dyspepsia: dyspeptic symptoms, patient investigated with a normal EGD; this term is used interchangeably with BERD and FD
➢	UD	- Uninvestigated dyspepsia: dyspepsia occurring in a person who has had no investigations

The lifetime prevalence of PUD is about 10% in North Americans. Chronic PUD is most commonly caused by *Helicobacter pylori* (*H. pylori*) infections and use of nonsteroidal anti-inflammatory drugs (NSAIDs) or ASA. Between 5 and 20% of patients with GU/DU have no evidence of either *H. pylori* or ASA/NSAID use, and may be due to rare conditions such as Zollinger Ellison syndrome (ZES)-associated gastrin-producing tumor, rarely DU or GU may be from Crohn disease or lymphoma, but about 25% have no known explanation (idiopathic). PUD may present with epigastric tenderness upon examination with other typical symptoms including nausea, vomiting, dyspepsia, bloating or burning epigastric pain which may be relieved by food or antacids. When the patient presents with (uninvestigated) dyspepsia, there are several approaches which may be taken (Table 2).

Table 2 Benefits and limitations associated with 5 interventional/ diagnostic approaches to the patient with dyspepsia who is under 50 years of age and who has no alarm symptoms

Diagnostic approach	Benefits	Limitations
o "Watchful waiting" only	-Patients with mild and transient symptoms are not prescribed medication or investigated	-No clinical studies
o Empirical Antisecretory therapy (PPI or H2RA)	-Addresses symptoms immediately -Documented effect on reflux and ulcer-related symptoms	-Recurrence after therapy is the rule -EGD is often only postponed, and may be falsely negative
o Treat based on clinical diagnosis	-Clinically meaningful -Low costs	-Unreliable
o Treat based on subgrouping and computer-based algorithms	-Clinically attractive -Low costs	-Does not reliably predict EGD diagnosis or response to therapy
o H.*pylori* test-and-treat	-Infected patients with ulcer disease will have symptomatic benefits -Reduces endoscopy rates. Safe and cost-effective compared with endoscopy -Possible reduced risk of later ulcer development	-Low benefit in those without peptic ulcer disease will not benefit -Continuing or recurrent symptoms may frustrate patients and clinician
o H.*pylori* test-and-scope	-Potential to reduce upper EGD rates in *H. pylori* low-prevalence areas	Only meaningful if a decision about eradication therapy in infected patients is influenced by endoscopy result -Increases endoscopy demands -Not applicable in *H. pylori*-high prevalence areas
o Early endoscopy	-Diagnostic "gold standard" -Might lead to reduced medication in patients with normal findings -Increased patient satisfaction in some trials	-Invasive. Costly -Low yield: About half of EGDs will be normal. -Long waiting lists may lead to false negative results because of previous therapy -Not the preferred option for many patients. -Does not diagnose non-erosive reflux disease (NERD)

Abbreviations: EGD, esophagogastroduodenoscopy; H2RA, H2 receptor antagonist; NERD, non-erosive reflux disease; PPI, proton pump inhibitor.

Adapted from: Bytzer P. *Best Practice & Research Clinical Gastroenterology* 2004; 18(4): pp.683.

In Canada, the recommended approach to the patient with undiagnosed dyspepsia is "The Hand." The physical may quickly determine the best approach to the patient with dyspepsia, based upon the response to five questions, representing the five fingers on the hand.

Table 3. Five questions to triage the patient with chronic uninvestigated dyspepsia

- o Symptoms due to non-upper GI conditions
- o Age >50, or alarm symptoms at any age
- o Use of NSAIDs/ASA
- o GERD—predominant symptoms
- o Possible *H. pylori* associated GI condition
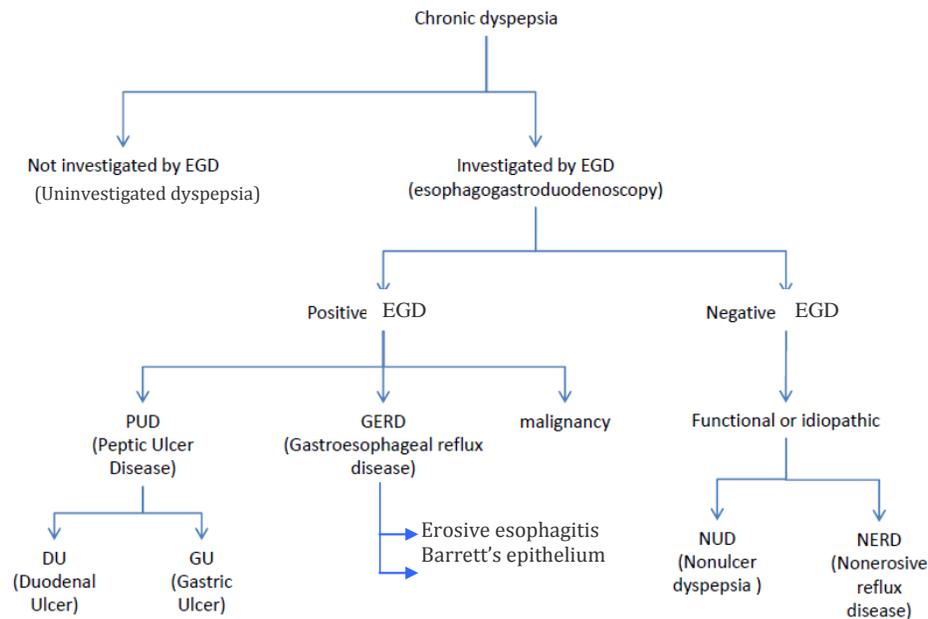
Figure 1. Terms used to describe Dyspepsia

History and physical examination

First exclude non-gastrointestinal sources of pain or discomfort in the upper abdomen, e.g., ischemic heart disease. If a non-GI condition is possible, stop and investigate. Determine if there are any "red flags" such as age more than 50 years, or at any age, abdominal mass, vomiting, bleeding, dysphagia, anemia or weight loss may be associated with rare but serious causes such as esophageal or gastric cancer (unfortunately, the stage of these malignancies is usually so far advanced when the patient presents that empirical treatment of dyspepsia for 4-8 weeks does not make the bad prognosis worse). If a patient is >50 years, if there are alarm symptoms, or if there is a history of esophagogastric malignancy-arrange for EGD.

Next, inquire if the patient is taking dyspepsia-causing medications, such as NSAIDs, ASA, antiplatelet drugs, or biphosphonates. If the answer if "yes," attempt to stop the possibly offending medication, and treat with PPI od for 4-8 weeks. If symptoms persist, arrange EGD. Ithe answer is "no," identify those with predominant reflux-like symptoms because they are more likely to respond to empiric PPI therapy for 4-8 weeks. For the person with uninvestigated dyspepsia (UD) who does not respond to lifestyle changes, avoidance of gastric irritant drugs (e.g. NSAIDs), and who does not respond to a 4-8 week course of PPI, the next step is to arrange for an urea breath test (UBT) to determine the possible presence of an H.pylori infection. The test-and-treat (for *H. pylori*) approach assumes that a DU/GU (if present) is responsible for the dyspeptic symptoms and is caused by *H. pylori*. A diagnostic test is performed for *H. pylori* and patients with positive test results are treated with triple therapy (PPI plus 2 antibiotics; see later section). About 90% of patients with DU and 70% of those with GU may be *H. pylori*-positive, although the association may be less striking in community practice, or in patients with a past history of an ulcer complicated by bleeding. The advantage of this strategy is that the investigations needed to diagnose *H. pylori* produce rapid results and can be readily used by the family physician, when available in the community. The disadvantage is that serology is not reliable unless it is negative, and UBT is not universally available in Canada, and the cost of these tests may not be covered by provincial health care plans. Note that in patients with *H. pylori* infection or normal EGD the benefit of eradication is small (7% to 15% symptom resolution).

If PPI therapy is ineffective then the clinician may consider a UBT, endoscopy or referral. Long-term healthcare costs are estimated to be approximately the same regardless of which investigative approach is followed.

The nonradioactive ^{13}C UBT (rather than the radioactive ^{14}C UBT) is recommended for use in children and women of child-bearing age.[1] Patients should be off antibiotics and bismuth for 1 month and proton pump inhibitor (PPI) or histamine H2-receptor antagonist (H2RA) for at least one week prior to the breath test. These drugs may suppress growth of the *H. pylori* sufficiently to produce a false negative result. IgG serology is appropriate if there is no access to UBT or endoscopy. If the serology is negative, the patient is truly *H. pylori* negative. A 20% decline in IgG serology titer over 6 months correlates with successful eradication of *H. pylori*. The necessary wait of 6 months duration prior to repeat testing and the need to save and compare the sera has taken the utility of serology testing out of favour. Although prompt endoscopy is the most sensitive and specific means to diagnose the cause of dyspepsia, it would be most appropriate in dyspeptic patients with one or more of the following characteristics: age >50 years, alarm symptoms (vomiting, bleeding, anemia, weight loss, dysphagia), GU detected on an upper GI series (i.e., to obtain biopsies to exclude gastric cancer).

The use of EGD to confirm healing of GU has fallen out of favour and can likely be skipped unless there is a strong suspicion that an ulcer is malignant (large size, or ongoing symptoms depite *H. pylori* eradication or PPI therapy). Upper GI barium study has an approximately 20% false-positive and false-negative rate for detection of ulcer disease and is generally not recommended, especially in those aged >50 years and in those with alarm features (see above).[2] However, barium studies are often more readily available than UBT or endoscopy and are still used to reassure the physician, but this negative upper GI barium atudy may be falsely negative and falsely reassuring. Of course, if the x-ray study shows an abnormality, this may help to facilitate the booking of a prompt EGD.

About a third of persons with dyspepsia may have lower abdominal complaints suggestive of the irritable bowel syndrome (IBS). Treatment of IBS may reduce the severity of the reflux symptoms, and enhance the person's quality of life.

Although emperic antisecretory therapy is relatively simple and non-invasive, endoscopy would permit the diagnosis of dyspepsia causes such as erosive esophagitis, Barrett's epithelium, GU or DU, gastric or duodenal erosions, *H. pylori* infection and gastric or esophageal cancer. Normal EGD results would be reassuring to both patient and physician. From a practical point of view, these advantages must be balanced against the disadvantages of EGD in the patient chronic dyspepsia.

Table 4. The disadvantages of EGD in the patient with chronic dyspepsia

- Scarcity of gastroenterologists to perform the procedure (the average waiting time to arrange for an EGD is 2 to 6 months),
- Cost (total cost approximately $500),
- Patient time lost from work
- Risk of complications such as aspiration or perforation (about 1 per 5000 procedures).

For empirical therapy, or for erosive esophagitis or NERD/NUD, start with od PPI. For patients who respond to initial PPI therapy, subsequent "on-demand" PPI therapy is more efficacious than continuous standard dose H2RAs but is not superior to on-demand H2RAs in H.pylori negative patients In patients who have completed their initial course of PPIs, continued PPI therapy is more efficacious than step-down to H2RAs for providing symptom relief. Standard dose PPIs are more efficacious than continued H2RAs in patients with uninvestigated GERD who have incomplete response to a previous trial of H2RAs. Approximately 20% of patients with UD will remain asymptomatic for up to 6 months after a successful course of initial therapy with PPI or H2RA. If dyspepsia symptoms persist, or if there are frequent recurrences, investigate with a UBT for *H. pylori* infection, or with prompt endoscopy. UBT for *H. pylori* is safe, effective, more comfortable and less distressing then endoscopy for the patient.[6]

Use of over-the-counter (OTC) therapy with antacids or H2RAs is common before patients seek medical advice. These drugs provide moderate benefit for mild symptoms of pain. Prescription doses of H2RAs relieve symptoms, but are much less effective for pain relief and ulcer healing than PPIs, and must be used twice daily and for longer periods (4 to 8 weeks for DU and 8 to 12 weeks for GU). Also, tachyphylaxis (loss of effectiveness over time) to H2RAs may develop quickly.

2. Peptic Ulcer Disease

Table 5. The secretory cells of the stomach, and chemical/peptide/hormone the cell secretes

- Goblet cell – mucus
- Parietal cell – HCl, intrinsic factor
- Chief cells - pepsinogen
- D cells – somatostatin
- G cells – gastrin
- Mast cells – histamine
- Enterochromaffin-like cells – histamine

Table 6. Clinical situations/syndromes which can be associated with fundic gland polyps

o *H. pylori* infection
o PPI use
o Hypergastrinemia
o Familial adenomatous polyposis (FAP; Attenuated FAP, 0.5-1.0% lifetime risk of gastric cancer)
o Cowden's syndrome
o Idiopathic

Table 7. Factors to consider when performing endoscopy in pregnant women

o A strong indication is always needed, particularly in high-risk pregnancies
o Whenever possible, endoscopy should be deferred until the second trimester
o The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)
o Procedure time should be short
o To avoid inferior venal cava or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
o Presence of fetal heart sounds should be confirmed before sedation and after the procedure
o Obstetric support should be immediately available
o No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)

Printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 435.

      An ulcer is defined as a break in the mucosa, which extends through the muscularis mucosae, and is surrounded by acute and chronic inflammation. The lesion of peptic ulcer disease (PUD) is a disruption in the mucosal layer of the stomach or duodenum. An ulcer is distinguished from an erosion by its penetration of the muscularis mucosa or the muscular coating of the gastric or duodenal wall. Peptic ulcer diseases result from an imbalance between protective (defensive) mechanisms of the mucosa and harmful (aggressive) factors (Table 8).

Table 8. Pathophysiological Factors Speculated to Contribute to Peptic Ulcer Disease

ProtectiveMucosal defence mechanisms	Harmful Aggressive factors
o Mucus secretion	o Acid/pepsin
o Bicarbonate production	o Bile acids
o Mucosal blood flow	o NSAIDs
o Cellular repair mechanisms	o *H. pylori* infection
o Prostaglandin E's	o Cigarette smoking
o Growth factors	o EtOH, stresses, coffee
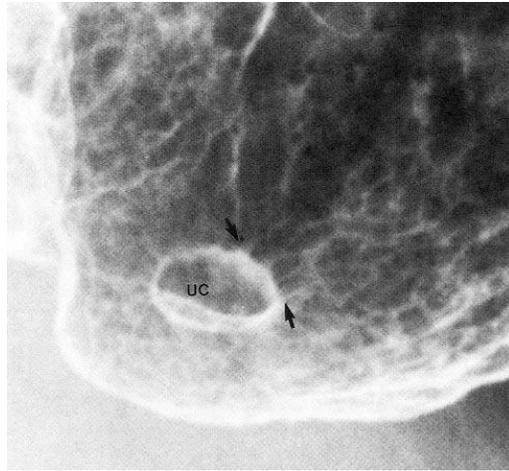
Figure 2. Benign gastric ulcer. Barium meal showing an ulcer crater (UC) situated on the greater curvature of the stomach, in the gastric antrum. The ulcer is visualized en face with a slightly oblique projection. Smooth mucosal folds radiating from the edge of the crater (arrows) in a regular fashion are a pathognomonic sign of a benign gastric ulcer. (Courtesy of Dr. J. Rawlinson.)


Figure 3. Penetrating gastric body ulcer (benign) in an asymptomatic elderly patient on NSAIDs.

2.1. Pathophysiological Factors

Given the multiple processes that control acid and pepsin secretion and defence and repair of the gastroduodenal mucosa, it is likely that the cause of ulceration differs between

individuals. Acid and pepsin appear to be necessary but not sufficient ingredients in the ulcerative process. It is clear that the majority of gastric ulcers (Figures 1, 3) and a substantial number of duodenal ulcers (Figures 4, 5, 6) do not have increased gastric acid secretion.
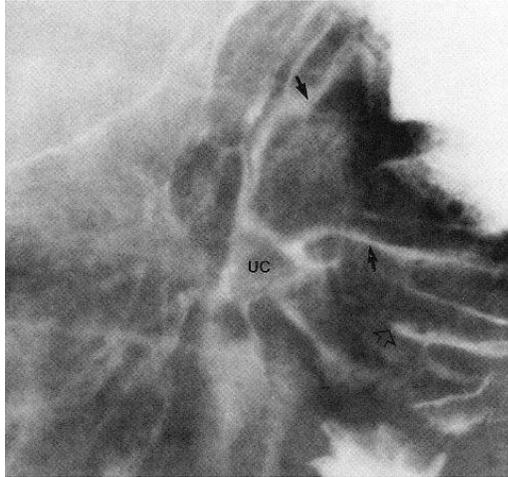
Figure 4. Malignant gastric ulcer. Barium meal demonstrating an ulcer crater (UC) on the lesseer curvature of the stomach, also visualized en face. In this case the radiating mucosal folds are irreg- ularly thickened (e.g., between closed arrows) and do not extend to the edge of the crater (open arrow) – features indicating a local infiltrative, malignant process. (Courtesy of Dr. J. Rawlinson.)

Peptic ulcers usually occur at or near mucosal transitional zones, areas that are particularly vulnerable to the deleterious effects of acid, pepsin, bile and pancreatic enzymes. Gastric ulcers are most commonly found on the lesser curvature, near the junction of acid-producing parietal cells and the antral mucosa, extending to an area 2–3 cm above the pylorus. Duodenal ulcers are usually found in the duodenal bulb, the pyloric channel or prepyloric area. Other peptic ulcers may occur in the esophagus, gallbladder (rarely, with ectopic gastric mucosa), and Meckel's diverticulum. Only one-third of DU patients have acid hypersecretion. Gastric acid production is usually normal in persons with gastric ulcers.

Table 9. Pathophysiologic defects in some patients with:

- ➤ Gastric ulcer disease
  - o Decreased acid secretion, decreased parietal cell mass (PCM), back-diffusion of acid
  - o Chronic superficial and atrophic gastritis
  - o Increased concentration of bile acids and pancreatic juice in stomach (duodenogastric reflux) Delayed gastric emptying
  - o Inappropriately decreased pyloric sphincter pressure under basal conditions and in response to acid (secretin) or fat (cholecystokinin) in the duodenum

- Duodenal ulcer disease
  - Increased parietal cell mass
  - Increased sensitivity of parietal cells to gastrin and secretagogues
  - Increased secretory drive
  - Decreased acid-induced inhibition of meal-stimulated gastrin release
  - Increased gastric emptying
  - Increased duodenal acid/pepsin loads
  - Chronic active gastritis

The most important contributing factors are *H. pylori* infection and NSAIDs, with each of these causing a disturbance in the balance between the protective and harmful factors (Table 8). The important topics of NSAIDs and *H. pylori* will be covered in later sections. In the person with PUD who is not on NSAIDs and who does not have an *H. pylori* infection, the cause of their ulcer disease is usually unknown (idiopathic). Although hypergastrinemia leading to acid hypersecretion, ZES, and possibly associated MEN-I is rare, this condition must be suspected in the person with severe/intractable PUD, multiple ulcers or ulcers at unusual sites, diarrhea, or adenomas of the pituitary or parathyroid (see previous chapter).

Duodenal ulcer is also associated with other illnesses such as hyper- pepsinogenemia I, systemic mastocytosis, MEN I, G-cell hyperfunction, rapid gastric emptying, childhood duodenal ulcer and immunological forms of pep- tic ulcer disease, glucocorticoid, chronic renal failure, renal transplantation, cirrhosis, chronic obstructive lung disease, and neurological trauma and burns (Curling's ulcer).

Heredity plays some role in peptic ulcer diseases, especially in DU. Twenty to 50% of patients with DU have a positive family history for PUD. Inheritance patterns of DU and GU appear distinct (i.e., DU—>DU and GU—>GU). Studies of twins show greater concordance among identical than among fraternal twins. In addition, individuals with blood group O have about a 30% increased risk of DU, compared with those of other blood groups
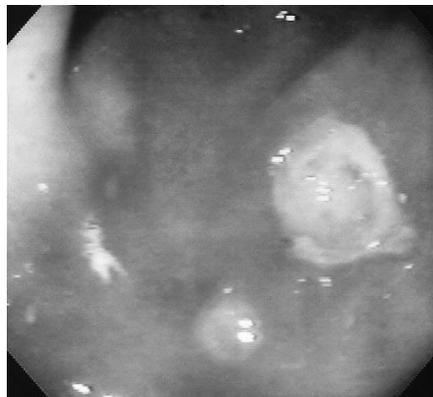
Figure 5. Duodenal ulcer, posterior wall.
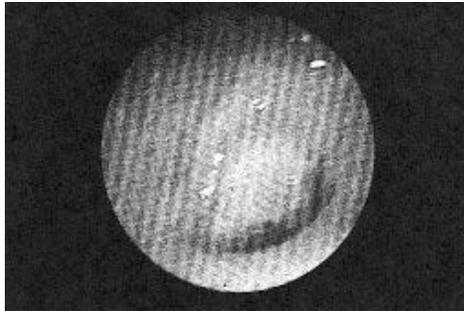
**Figure 6.** Duodenal ulcer. Endocopic view of the duodenal cap ulcer.

Figure 7. Duodenal ulcer situated at the base of the duodenal cap. The ulcer crater is filled with barium (arrow). The surrounding inflammatory process has considerably distorted the normal bulbar configuration of the proximal duodenum. (Courtesy of Dr. J. Rawlinson.)

2.2. *Helicobacter pylori and Peptic Ulcer Disease*
2.2.1. Introduction

The discovery that *H. pylori* infection is the main cause of peptic ulcer caused a paradigm shift in our understanding of the disease pathogenesis. This was the first example of a common chronic bacterial infection usually acquired in childhood causing disease much later in life. In the future, many other diseases are likely to be linked to chronic infections but for now *H. pylori* studies provide fascinating insights into long term bacterial-host interactions.
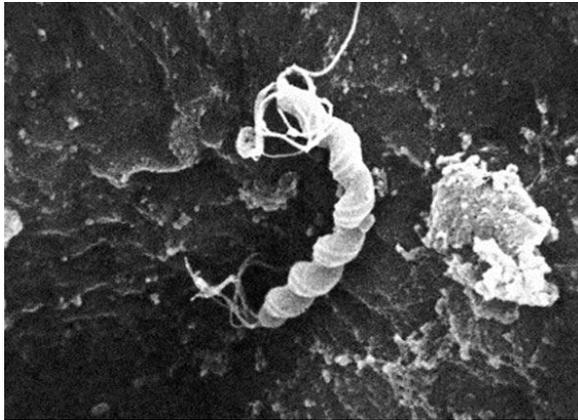
Figure 8. *Helicobacter pylori*. (Courtesy of McMaster University Medical Centre Electron Microscopy Lab.)

2.2.2. Epidemiology

Studies around the world suggest the prevalence of *H. pylori* infection is 90–95% in patients with duodenal ulcer, 80–85% in patients with gastric ulcer and approximately 50% in the general population and 30% in Canada. Ran- domized controlled trial data proves that this association is causal but this does not mean that 90-95% of all duodenal ulcers are due to *H. pylori*. As the prevalence in the general population is also high, a few ulcers that are not due to *H. pylori* infection will still have the infection by chance. It is estimated that about 75% of all peptic ulcers are attributable to *H. pylori* infection with most of the rest being due to nonsteroidal anti-inflammatory drugs. The lifetime risk of having an ulcer in individuals infected with *H. pylori* is difficult to calculate, but is probably between 10 and 15%. *H. pylori* represents 60% of the causative factors for gastric cancer, and approximately 1% of persons infected with *H. pylori* will develop gastric cancer (see next chapter).

2.2.3. Pathophysiology

H. pylori infection may cause or increase dyspepsia and its complications. It is important to stress that about 25% of Canadians have an H.pylori infection in their stomach, but in less than a quarter of this quarter is the infection associated with a symptomatic condition that responds to eradication therapy of the *H. pylori*. To rephrase, if the patient with an *H. pylori* infection has dyspepsia but non RU/GU, there is only a small likelihood that their dyspepsia will respond to eradication of the *H. pylori*. In sharp contrast, if the dyspeptic person has a peptic ulcer plus an *H. pylori* infection, eradicating the infection cures the ulcer disease and resolves symptoms in over 80% of sufferers. Furthermore, in persons with an *H. pylori* infection plus dyspepsia, *H. pylori* eradication decreases their dyspepsia score, but has no effect on the person's quality of life (Bektas et al, 2009).

H. pylori infection is the most common chronic bacterial infection worldwide yet only a small proportion of cases develop disease. The reasons for this are not fully understood but relate to a combination of environmental, host and bacterial factors. Certain strains of *H. pylori* are more likely to cause peptic ulcer disease. The most well characterized is the cytotoxin associated gene (cagA) and the vacuolating cytotoxin (vacA) gene. The cagA gene encodes for a cagA protein that is

injected into the host epithelial cells to induce changes in the gastric cytoskeleton. All strains possess the vacA gene but the s1m1 variant has the most potent cytotoxic activity and highest risk of causing pep- tic ulceration. Contact with epithelial (iceA) gene is another virulence factor with the iceA1 genotype, and is associated with increased gastric inflamma- tion and higher likelihood of disease. Peptic ulceration is not universally pre- sent even with the most pathogenic strains of *H. pylori* and other factors such as male gender, host genetic factors (such as those that predict gastric acid output) and smoking will influence whether the infection causes disease.
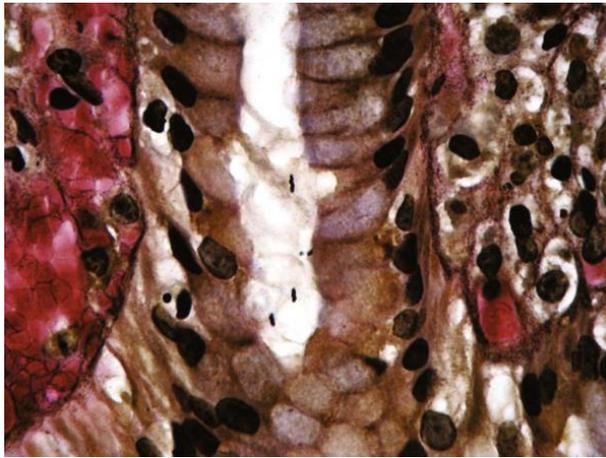
Figure 9. Photomicrograph of a gastric mucosal biopsy specimen, stained with the Genta stain, from a patient with *Helicobacter pylori* gastritis. The bacteria are well seen.

Another epidemiological paradox is how an infection can cause both gas- tric and duodenal ulcer disease yet both types of ulcer rarely exist in the same patient. The distribution of infection in the stomach appears to be the most important determinant of disease phenotype. Duodenal ulceration most likely occurs when there is an antral predominant *H. pylori* infection that decreases antral somatostatin production. This reduces the negative inhibitory effect on gastrin production by antral G cells. The increased gastrin production increases parietal cell mass and acid output. The excess acid entering the duodenum causes the mucosa to undergo gastric metaplasia that can in turn be infected with *H. pylori*. The organism then causes inflammation, epithelial injury, and reduces duodenal bicarbonate secretion. This compro- mise to duodenal mucosal defence predisposes to ulcer formation.

In contrast, *H. pylori* infection is more likely to cause gastric ulceration if the infection is more evenly spread throughout the stomach. The pangastritis that results will cause inflammation of parietal cells and overall gastric acid secretion will be reduced. The inflammation will also impair mucosal defence and this can result in gastric ulceration even in a relatively hypochlorhydric environment.

The distribution of *H. pylori* is predicted by environmental factors. Acid output has yet to reach full capacity in the neonatal period so if *H. pylori* is acquired soon after birth it will be able to infect the whole stomach causing a pan-gastritis. This is probably exacerbated by the poor nutrition seen in many developing countries. If the infection is acquired later in childhood

when acid secretion is higher, *H. pylori* will prefer to reside in the antrum where less acid is produced.
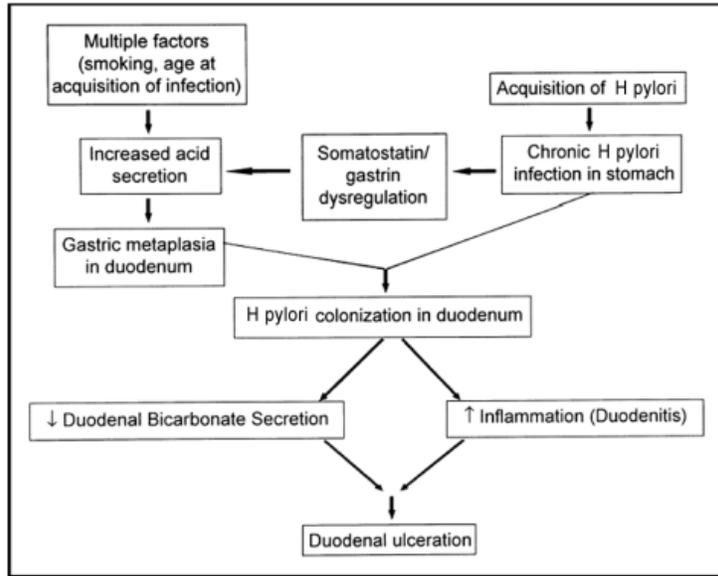
Figure 10. Model of duodenal ulcer pathogenesis. Persons infected with cagA/tox /*H. pylori* strains develop enhanced mucosal inflammation, which may lead to heightened gastric acid secre- tion with development of gastric metaplasia, colonization by *H. pylori* in the duodenum, and sub- sequent duodenal ulcer formation.

The urease activity of *H. pylori* provide a means for the organism to burrow through the mucus overlying the gastric epithelium to bind to adhesions, and to calorize the alkaline environment adjacent to the membrane. It invades the gastric mucosa, while being able to evade the host immunity. The adhesions provide an interplay between bacterial and List Lewis antigens, and help to determine different clinic-pathologic outcomes (Sheu et al. 2010). IL-1 and TNF-α gene clusters are important in defining the extent and severity of *H. pylori* associated gastritis. The common pan-gastritis may or may not be symptomatic, the antral predominal gastritis is associated with an increased risk of duodenal ulcer disease, and gastric body associated gastritis is associated with multifocal gastric atrophy and an increased risk of gastric cancer (Shanks and El-Omar 2009). *H. pylori* is thought to be transmitted by the gastro0oral or the fecal-oral route. If one family member has an *H. pylori* infection, it has an impact on other family members and the community (Table 10).

There is a broad range of tests available to diagnose the presence of an *H. pylori* infection, put only upper endoscopy plus biopsy for histological examination or culture will provide a diagnosis of *H. pylori* plus *H. pylori* associated disease such as gastritis, peptic ulcer disease intestinal metaplasia, gastric cancer or mALT lymphoma (Guarner et al. 2010). The culture of the gastric biopsies also provides for testing for in vitro antibiotic sensitivity of the organism, as well as gene testing for antibiotic resistance, but the sensitivity is low. The rapid

urease tests have better sensitivity than less histology. The non-tissue, non-endoscopy tests include blood, breath and stool antigen testing. The urea breath test is more than 75% sensitive and can be used both to diagnosis an *H. pylori* infection and to confirm its eradication. Testing for *H. pylori* antigens in stool is also useful before and after treatment, and has a greater than 95% sensitivity.

Table 10. The impact of one person in the family being positive for *H. pylori* on the rate of *H. pylori* infection by others in the family

- Hp positive parent
  - spouse 68% Hp^+
  - children 40% Hp^+

- Hp negative parent
  - spouse 9% Hp^+
  - children 3% Hp^+

- Community Risk
  - Adults - approximately 25-30% (depends on person's age)
  - Higher (30%) in older persons
  - >50% First Nations Canadians, new Canadians originally from high Hp prevalence areas
  - New Canadians from high prevalence countries

Table 11. Indications for Testing and Treatment of *Helicobacter pylori* infection

- Supported by evidence
  - Active peptic ulcer disease (gastric or duodenal ulcer)
  - Confirmed history of peptic ulcer (not previously treated for *H. pylori* infection)
  - Gastric MALT-lymphoma (low grade)
  - Following endoscopic resection of early gastric cancer
  - Uninvestigated dyspepsia (if *H. pylori* population prevalence high)

- Controversial
  - Functional dyspepsia
  - GERD
  - Persons using NSAIDs, especially when first initiating NSAID treatment
  - Unexplained iron deficiency anemia or immune thrombocytopenic purpura
  - Populations at higher risk of gastric cancer (ie. Asians, Eastern Europeans, Mesoamericans)

GERD, gastroesophageal reflux disease; MALT, mucosa-associated lymphoid tissue; NSAIDs, nonsteroidal anti-inflammatory drugs.

In persons with an *H. pylori* infection plus dyspepsia, *H. pylori* eradication decreases their dyspepsia score, but has no effect on the person's quality of life (Bektas et al. 2009).

There are many conditions in the GI tract which are associated with *H. pylori* infection, the most important of which are dyspepsia, peptic ulcer disease, and gastric cancer (Table 12).

If the patient is *H. pylori*-positive, treat with triple therapy (PPI plus 2 appropriate antibiotics taken bid for 7–14 days). It is not always necessary to continue the PPI for longer. After the patient has been off PPI for 2 weeks, perform a urea breath test (UBT).[29] If the *H. pylori* has cleared, a delayed second UBT should be performed to completely exclude *H. pylori* infection[30], in which case PPI maintenance therapy would not be required. If the *H. pylori* has not cleared, a different triple therapy, or quadruple therapy would be needed, and the UBT is repeated to prove eradication of *H. pylori*. If the ulcer is not associated with *H. pylori*, or if the use of ASA or NSAIDs cannot be stopped, continue PPI maintenance therapy for life to reduce the risk of rebleeding.

Table 12 - GI and non-GI conditions which may be associated with *H. pylori* (Hp) infection

- ➢ Hp-associated GI Diseases
    - o Non-ulcer dyspepsia
    - o Acute/chronic gastritis
    - o Atrophic gastritis – intestinal metaplasia- dysplasia – GCa (gastric cancer [non-cardia])
    - o Duodenal and gastric ulcer (DU and GU) (only ~20% of Hp$^+$ persons develop disease)
    - o Accentation of effect of smoking on PUD
    - o Accentuation of ASA/NSAID effects on peptic PUD
    - o Maltoma
    - o Fundic gland polyps
    - o Hypertrophic gastric folds
    - o Protective against GERD (possible)
    - o Halitosis
    - o Carcinoid tumors
    - o Colorectal cancer (possible)
    - o Pancreatic cancer (possible)

- ➢ Possible Hp-associated non-GI diseases
    - o Head –otitis media, migraines, headaches
    - o CNS – Parkinsonism, CVA
    - o Heart – atherosclerotic diseases
    - o Lung – chronic bronchitis, COPD, SIDS
    - o Blood – ITP, iron deficiency
    - o Skin – idiopathic chronic urticaria, acne, rosacea
    - o Growth retardation in children

Abbreviations: CVA, Cerebrovascular accident; COPD, chronic obstructive pulmonary disease; DU, duodenal ulcer; GCa, gastric cancer; GERD, gastroesophgeal reflux disease; GU, gastric ulcer; ITP, idiopathic thrombocytopenic purpura; PUD, peptic ulcer disease; SIDS, sudden infant death syndrome.

Adapted from: Hunt R. *AGA Institute Post Graduate Course* 2006; page 333-342.; and adapted from Graham DY. and Sung JJY. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006. page 1054.

Table 13. Recommended indications for *H. pylori* eradication therapy (ET) in the patient taking NSAIDs or ASA

Level of recommendation	Strength of Advice	
➤ Advisable	2	o Reduce PUD formation
➤ Strong	2	o Reduce recurrent PUD
➤ Strong	1	o Reduce recurrent PUD bleeding (in ASA or NSAID high risk users)
➤ Advisable	2	o ET does not prevent further PUD bleeding in high risk ASA/NSAID users on PPI

Modified from Lai LH & Sung JJY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(2): page 270.

Table 14. The annual incidence of NSAID-induced adverse event can be estimated by multiplying the baseline absolute risk (AR) with patient-specific relative risk modifiers

➤ Risk characteristic		
o Baseline absolute risk (AR) for GI event (%) -2.5 (1.5-4.5%)		2.5
o Increase in risk:	Age >65 years	2.5
	Use of anticoagulants	2.5
	Use of steroids	2.0
	History of PUD	5.0
	High dose of NSAIDS	2.0
	Presence of *H. pylori*	1.5
o Reduction in risk:	Therapy with PPIs	0.5

Printed with permission: Lanza FL, et al. *The American Journal of Gastroenterology* 2009;104:734.

2.2.4. Treatment

Peptic ulcers can be healed by acid suppression with a PPI or H2RA, but about 80% recur once anti-secretory therapy is discontinued. The strongest evidence that *H. pylori* infection causes peptic ulcer comes from randomized controlled trials that show eradication of the organism permanently cures the disease in most cases. Indeed antibiotic therapy alone can cure duodenal ulcer without the need for acid suppression. This evidence has led major guidelines worldwide to recommend *H. pylori* eradication therapy in infected patients with gastric and duodenal ulcer disease. Indeed, the relapse rate for duodenal ulcer disease after healing with acid suppression is 64% over 3–12 months. This falls to 14% in those receiving *H. pylori* eradication therapy. The relapse rate for gastric ulcer is 40% compared with 12% after *H. pylori* eradication. The number needed to treat (NNT) to prevent the recur- rence of a duodenal ulcer was 2 (95% CI = 1.7 to 2.3). This is a very dramatic effect compared with the NNT for most other diseases but actually underesti- mates the true impact of *H. pylori* eradication, as many of the therapies included in the systematic review were substandard. When only proton pump inhibitor-based triple therapies or

bismuth salt quadruple therapies were included, the relapse rate for duodenal ulcer patients fell to 8%. Many of the patients who relapsed still harboured *H. pylori* but a few patients had an ulcer relapse despite being *H. pylori* negative. This relates to the epidemiology of the association. If *H. pylori* is common, then a few patients will develop peptic ulcer disease through other causes and be infected by chance. Eradication of the organism in this setting will not cure the ulcer diathesis. A positive UBT is a surrogate marker for PUD (DU or GU), and eradication of this infection will remove this cause of PUD and its symptoms. Eradication of *H. pylori* will also reduce the adverse effects of NSAIDs and smoking on the mucosa of the stomach and duodenum.

Duodenal ulcer is typified by *H. pylori* infection and duodenitis and in many cases impaired duodenal bicarbonate secretion in the face of moderate increases in acid and peptic activity (Figure 7). The increased acid load resulting from *H. pylori* infection of the antrum is delivered to the duodenum, causing damage to the duodenal mucosa and eventually leading to the devel- opment of gastric metaplastic lesions. *H. pylori* bacteria can infect these islands of gastric mucosa, and the combination of increased acid delivery and *H. pylori* infection ultimately leads to ulcer formation (Figure 10). Gastric ulcer often occurs with decreased acid-peptic activity, suggesting that mucosal defensive impairments are more important.

Thus, the treatment of peptic ulcer disease associated with an *H. pylori* infection is the eradication of *H. pylori*.

H.pylori eradication has benefits beyond the relief of the dyspepsia. These benefits include the removal of the approximately 15% lifetime risk of PUD, and 1% risk of developing gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma if the infection is left untreated. Treatment regimens approved by the Canadian Helicobacter Study Group achieve a minimum eradication rate (on an intention-to-treat basis) of at least 80%. First-line triple therapy consists of a PPI plus two antibiotics (clarithromycin and either amoxicillin or metronidazole) administered twice daily for one week (Table 1). Quadruple therapy is also considered to be a first-line treatment.

A prepackaged triple therapy combination containing lansoprazole, clarithromycin and amoxicillin trihydrate is commercially available as Hp-PAC®. PMC (PPI plus metronidazole and clarithromycin) prepackaged combination is not available commercially. The prevalence of Metronidazole-resistant *H. pylori* in Canada is about 20% and resistance to amoxicillin is less than 1%, thus use of amoxicillin-containing regimens is increasing.

If one triple-therapy regimen fails to eradicate *H. pylori*, the patient should be re-treated with a different antibiotic combination, for two weeks rather than one, or with a quadruple therapy (PPI, bismuth, metronidazole plus tetracycline) rather than triple therapy. With increasing prevalence of resistance of H.pylori to treatment with metronizadole or clarithromycin, second line therapy is increasingly required, including levoflaxacin.After successful *H. pylori* eradication, the risk of re-infection is only about 1% per year.

All PPIs have similar efficacy in triple therapy regimens for H.pylori eradication. Twice daily PPI dosing, however, is more efficacious than once daily dosing (when used in a PAC or PMC triple-therapy regimen). *H. pylori* eradication therapy with triple therapy (PAC and PMC) for 7 days is as efficacious as therapy for 10 or 14 days. H.pylori eradication therapy with triple therapy (PAC and PMC) for 10 days is as efficacious as 14 days. Continued treatment with a PPI after a course of H.pylori eradication therapy does not produce higher ulcer healing rates than eradication therapy alone in infected patients with uncomplicated DU. This does not apply to GU,where PPI therapy for 6-8 weeks is recommended.

The discovery of *H. pylori* has changed the life cycle of peptic ulcer disease (PUD).

However, PUD does not completely disappear after elimination of *H. pylori* infection. Some ulcers recur even after successful eradication of *H. pylori* in non-NSAIDs users. In addition, the incidence of *H. pylori*-negative, non-NSAID PUD (idiopathic PUD) is reported to increase with time. More- over, *H. pylori*-positive ulcers are not always *H. pylori*-induced ulcers because there are two paradoxes of the *H. pylori* story: the existence of H. pylori-positive non-recurring ulcer, and recurring ulcer after cure of *H. pylori* infection. Taken together, it is clear *H. pylori* infection is not the only cause of peptic ulcer disease. Therefore, it is still necessary to consider the pathophysiology and the management of the ulcers, which may exist after elimination of *H. pylori* infection.

Table 15. Useful Background: *H. pylori*

o Meta-analysis does not show a statistical difference in *H. pylori* eradication rates using wither triple quadruple therapy (RR = 1.002; 95% Cl 0.936-1.073) (Luther J Schoenfeld P, et al. The American Journal of Gastroenterology2008: S396).

o Meta-analysis shows 93% ER with sequential therapy versus 74% for clarithromycin-based triple therapy (Jafri N, et al. Annals of Internal Medicine 2008: 2220-2223), particularly in persons with clarithromycin-resistant strains of *H. pylori*, but non of the *H. pylori* treatment guidelines (yet) endorse sequential therapy (Chey 09).

o Met-analysis has shown superiority of a 10-day course of levofloxacin-based triple therapy is a 7 day course of bismuth-based quadruple therapy (rr = 0.51; 95% Cl: 0.34-0.75) for persistent *H. pylori* infection (Saad R Schoenfeld P, et al. The American Journal of Gastroenterology2006: 488-96)

o Rifampin has been used as an alternative to alrithromycin, with ER of 38-91% (Chey WD, Wong BC. The American Journal of Gastroenterology2007: 1808-1825) but there may be rare but serious adverse effects (myelotoxicity and ocular toxicity).

o Furazolide used in place of clarithromycin, metrondiazole or amoxicillin gives ER of 52-90% (Chey WD, Wong BC. The American Journal of Gastroenterology2007: 1808-1825).

To ensure eradication of *H. pylori*, UBT or endoscopic biopsy may be repeated at least 30 days after completion of eradication therapy. Retesting may be particularly important if patient suffered of complicated ulcers (bleeding or perforation). It may also be necessary to prove that eradication has occurred before looking for new causes of dyspepsia in the occasional patient who experiences recurrent dyspepsia after the use of an approved eradicative regimen.

3. NSAIDs, Coxibs, ASA

NSAIDs can cause damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect of these drugs on the epithelium, impairment of the barrier properties of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury (Figure 8, 9). In addition, the presence of acid and, in some cases, *H. pylori* infection in the stomach and duodenum may contribute to the ability of NSAIDs to damage the mucosa.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin are among the most widely prescribed effective drugs for the treatment of pain and inflammation. The use of NSAIDs, however, is a well-known cause of gas- trointestinal (GI) adverse events, including

dyspepsia, abdominal pain, nau- sea, erosive gastroduodenitis, ulceration, perforation, hemorrhage and even death. Nearly all patients who take aspirin or traditional NSAIDs develop asymptomatic acute upper GI tract injury (erosions or ulcers) at some point in time. Interestingly, very few patients who develop serious complications have antecedent dyspeptic symptoms. Treatment of GI events caused by NSAIDs is also costly. Studies have shown that for each dollar spent on NSAIDs, an additional 55–125% is needed to treat GI events. Risk factors for serious GI complications are outlined in Table 5. This risk stratification is important to determine in every person on NSAIDs, so that the selection of which NSAID/Coxib may be established, and protective therapy with a proton pump inhibitor (PPI) may be prescribed ("co-therapy").

Table 16.   Risk factors for serious GI events associated with NSAID use

Clinical risk factors	Drug risk factors	Social risk factors
o Advanced age	o Individual NSAID risk	o Smoking
o History of ulcer or ulcer complications	o High dose intake	o Alcohol
	o Multiple NSAIDs	
o Major illness (e.g., heart disease, type & severity of arthritis)	o Concomitant corticosteroid	
o Severe comorbidity & disability	o Concomitant anticoagulant/ antiplatelet drugs	
o *H. pylori* infection		

Although the mechanisms by which NSAIDs cause mucosal damage are not completely clear, they involve both topical injury and systemic effects. The complex elements that defend the gastroduodenal mucosa from damage are largely dependent on endogenous prostaglandins (PGs) synthesized in the GI mucosa. The two known isoforms of cyclo-oxygenase (COX), COX-1 and COX-2, direct the synthesis of PG from arachidonic acid. COX-1 is constitu- tively expressed in most cells and plays an important role in the GI mucosal protection, renal blood flow regulation and normal platelet function. In con- trast, COX-2 is largely inducible by inflammation and is thought to generate prostaglandins that are responsible for pain and inflammation. In general, non-selective NSAIDs inhibit both COX-1 and COX-2 pathways leading to both beneficial (mucosal defense) and toxic outcomes. It has been postulated that the injurious effects of NSAIDs are due to the inhibition of COX-1 and loss of GI mucosal protection, and also due to increased risk of bleeding through inhibition of platelet function. There is a correlation between the risk of GI complications and the relative degree of inhibition of COX-1 and COX-2 isoenzymes. An NSAID with higher selectivity for COX-2 than COX-1 is associated with significantly less GI toxicity than other non-selective NSAIDs. The premise that preferential inhibition of COX-2 would maintain the therapeutic benefit of traditional NSAIDs with less GI toxicity due to spar- ing of COX-1 led to the development of more-selective COX-2 inhibitors. First generation coxibs (celecoxib and rofecoxib), and second generation cox- ibs (etoricoxib, valdecoxib, parecoxib and lumiracoxib) have improved GI tolerance and less adverse events across a range of different GI safety assessments. In clinical trials, coxibs significantly reduced the risk of ulcers and ulcer complications compared to non-selective NSAIDs.

The safety profile of NSAIDs is variable and dependent on the class of NSAID with the selective COX-2 inhibitor class being among the safest. Aspirin doses as low as 10 mg/day can cause ulcers. Long-term use of aspirin alone is associated with 1.5–3 times increase in risk of GI complications even when used at low-dose (≤ 150 mg daily) or buffered or as enteric-coated formulations. The use of traditional non-selective NSAIDs increases the risk of serious GI complications by approximately 2.5–5-fold compared with patients not receiving these medications. There is a 2–4-fold increase in risk when low-dose aspirin is added to a non-selective NSAID compared to the use of low-dose aspirin alone. Among the classic NSAIDs, ibuprofen and etodolac are the least toxic. Naproxen, indomethacin, aspirin and diclofenac have intermediate toxicity, whereas ketoprofen and piroxicam are among the most toxic to the GI tract.
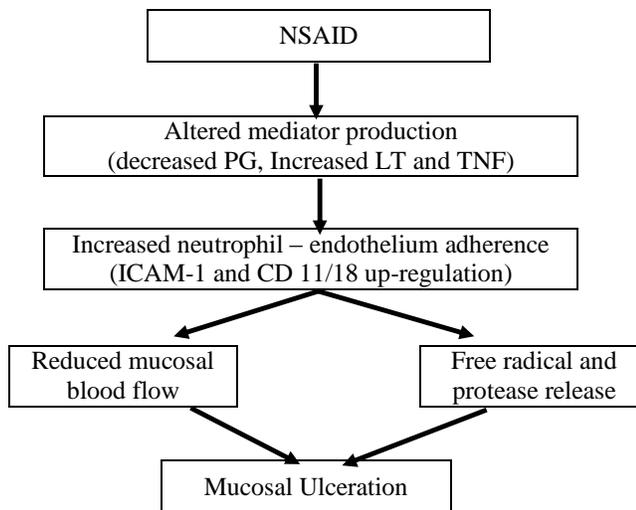
Figure 11. Role of changes in the gastric microcirculation in the pathogenesis of NSAID-induced ulceration. NSAIDs suppress prostaglandin (PG) synthesis, and cause an increase in the liberation of leukotriene (LT) B4 and tumour necrosis factor (TNF). The net result is an increase in expression of various adhesion molecules, leading to neutrophil adherence to the vascular endothelium.

The prevalence of ulcer complications such as upper GI hemorrhage has not declined in the past decade, although *H. pylori* infection is declining in our Canadian population. Ulcer complications remain, mainly because of the aging population and increasing prevalence of arthritis, which is leading to an increased consumption of NSAIDs. To protect patients at risk, several strate- gies are advised, including the use of the lowest effective dose of NSAIDs, concomitant use of gastroprotective agents (e.g., acid antisecretory drugs, pro- ton-pump inhibitors, or mucosal protective drugs) or alternative treatment with a coxib. Prevention of GI events is in particular indicated among patients with risk factors who require long-term treatment with NSAIDs, and use of a coxib and co-therapy with a PPI are the two most cost-effective treatments to decrease the risk of hospitalization for serious events (Table 17). The coxibs have decreased the risk of developing GI clinical events and complications in high-risk patients by

more than 50% in large clinical trials. When economically possible, a coxib alone is preferable to a conventional NSAID plus a gastroprotective agent, but patients at high risk require a gastroprotective agent in addition to a coxib.

Table 17. Selection of NSAIDs and GI protective agents based on the key clinical factors

Risk of GI NSAID event	
Low	Average / high
➢ Not on aspirin, NSAID alone	o Coxib or NSAID+PPI
➢ On aspirin, NSAID + PPI or coxib	o NSAIDs +PPI or coxib +PPI

When deciding to place a patient on an NSAID, risk stratification must take into account the GI and renal risks, the presence of *H. pylori*, and importantly also the cardiovascular risks (Gupta and Eisen 2009). The use of an NSAID plus PPI, a COX-2 inhibitor, or a COX-2 inhibitor plus PPI does not prevent damage to the small or large intestine. The importance of cardiovascular risk of Coxibs became apparent with the APPROVE study. In the patient with both high GI and cardiovascular risk, an NSAID is given with ASA and a PPI. *H. pylori* is an independent and additive risk factor to the risk of NSAIDs and needs to be addressed (Table 18). Begin by taking a careful a drug history for NSAID/ASA use, including low-dose ASA for cardioprotection, as well as other medications that may cause or aggravate dyspepsia, e.g., bisphosphonates, tetracyclines, calcium channel blockers.
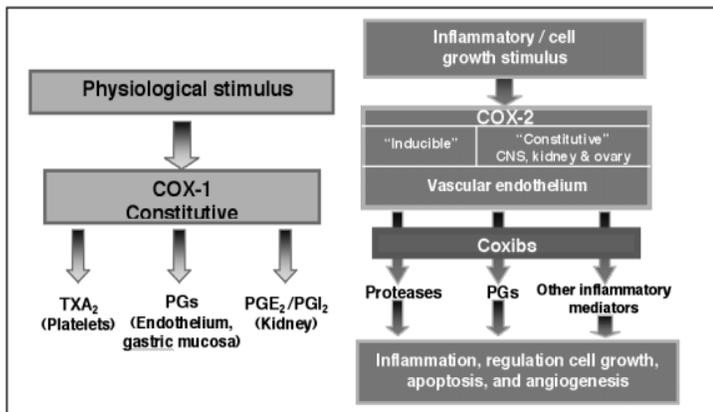
Figure 12. Proposed roles of the two known isoforms of COX and role of coxibs TXA$_2$, thrombozane A2; PGE2: prostaglandin E2; PGs: prostaglandins; PGI2: prostacycline; coxibs: COX-2 inhibitors.

Table 18. Reasons for *H. pylori* eradication therapy (ET) in the patient taking NSAIDs or ASA

- o Reduce PUD formation
- o Reduce recurrent PUD
- o Reduce recurrent PUD bleeding (in ASA or NSAID high risk users) (ET does not prevent further PUD bleeding in high risk ASA/NSAID users on PPI)

Abbreviation: ET, eradication therapy
Adapted from: Lai LH., and Sung JJY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(2): page 270.

The vulnerable inflammatory phenotype of atherosclerosis is associated with a Th1 type immune response. The traditional NSAIDs and selective COX-2 inhibitors enhance this Th1 response by reducing prostanoids and promoting por-atherogenic cytokines and plaque instability. It is proposed that this is the mechanism by which these classes of drugs enhance the cardiovascular risk (Padol and Hunt 2009; Rainsford 2010).

An expert panel has developed an algorithm to guide us in the appropriate use of PPIs, NSAIDs, and ASA in those persons with high-or-low-risk of gastrointestinal cardiovascular disease (Alimentary Pharmacology expert panel, 2009). Gastrointestinal risk was stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants) (Table 19 and 20). High CV risk was arbitrarily defined as the requirement for low dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H.Pylori*, and if the infection is present, eradication therapy should be given. The practitioner must become familiar with the appropriate class of medication to use based on the GI plus CVS.

Table 19. GI risk stratification for NSAID GI toxicity

➤ High risk
- o History of a previously complicated ulcer, especially recent
- o Multiple (>2) risk factors

➤ Moderate risk (1-2 risk factors)
- o Age >65 years
- o High dose NSAID therapy
- o A previous history of uncomplicated ulcer
- o Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants

➤ Low risk
- o No risk factor

Abbreviations: CV, cardiovascular risk; NSAIDs, Nonsteroidal anti-inflammatory drugs
Printed with permission: Lanza FL, et al. *The American Journal of Gastroenterology* 2009;104:734.

Table 20. Recommendations for avoiding peptic ulcers (gastric or duodenal) associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a function of low, moderate and high gastrointestinal, as well as low and significant cardiovascular risk (CV) (e.g. required use of ASA plus NSAID)

	Low GI Risk	Moderate GI Risk	High GI Risk
➢ Low CV Risk (no ASA)	o An NSAID with a low ulcerogenic potential at the lowest effective dose o Avoid multiple NSAIDs	o NSAID plus PPI o Misoprostol o COXIB	o COXIB plus PPI o Misoprostol
➢ Significant CV Risk (requires ASA)	o NSAID plus a PPI	o A combination of an NSAID and a PPI	o Avoid NSAIDs and COXIB

Abbreviations: COXIB , COX-2 inhibitor; CV, cardiovascular risk; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Printed with permission: Lanza FL, et al. *The American Journal of Gastroenterology* 2009; 104: pg 728-38.

Over a one-year interval, about 3% of NSAID users will develop a GU/DU. The possibility of NSAID-induced gastric complications should be discussed with patients, including the signs and symptoms of GI bleeding, e.g., dyspepsia, coffee ground emesis, melena. Patients at high risk may be offered gastric protective therapy with standard doses of PPI. Alternatively, misoprostol 200 μg QID may be offered, but the tolerability of this agent is limited by GI adverse effects.[18] The risk of developing an NSAID-associated ulcer is greater in persons over the age of 65, in those who use more than one NSAID, higher doses of NSAIDs, in patients receiving concomitant steroids or anticoagulants, and in those with a history of ulcer disease and coexisting ischemic heart disease. Patients taking ASA with an NSAID are also at higher risk of ulcer complications. There is an additive effect between *H. pylori* infection and use of NSAIDs on the development of peptic ulcer and ulcer bleeding.[19] For this reason, many experts recommend that persons beginning long-term NSAIDs should be screened for *H. pylori* and treated if found to be positive (Table 21).[1] Compared to regular NSAIDs, COX-2 inhibitors may reduce the risk of complicated peptic ulcer bleeding by 50 to 70%.[15,16,17] However, reports of cardiovascular complications with use of COXIBs have limited their use and challenged their safety. Standard dose PPI therapy for 4-8 weeks produces higher healing rates in NSAID-associated ulcer than H2RAs or 800 mcg misoprostol when NSAIDs are continued. Whenever possible, the NSAID should be stopped. Standard dose PPIs are more efficacious than standard dose H2RAs or 400 mcg misoprostol (but not 800 mcg misoprostol) for the prevention of NSAID-associated gastric and duodenal ulcers. There is no difference in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding. Continuous acid inhibition, preferably with a PPI, may be needed in select patients with DU/GU not associated with *H. pylori* infection. This is especially true when the ulcer is complicated by bleeding or perforation, or when the patient continues ASA/NSAID use or experiences frequent recurrences of dyspepsia.

Table 21. Key points to consider regarding NSAIDs and gastroprotection

- ➢ Concomitant PPI use reduces the risk of development of NSAID induced endoscopic lesions such as ulcers
- ➢ Concomitant PPI use is strongly recommended for high risk NSAID users
- ➢ It is not known whether concomitant PPI use reduces the risk of clinically significant GI events such as hemorrhage and perforation
- ➢ PPI co-therapy in high risk NSAID users is equivalent to COX-2 therapy in preventing NSAID induced endoscopic lesions
- ➢ PPI used is effective as secondary prevention of ulcer complications in patients needing antithrombotic therapy with aspirin or clopidogrel
- ➢ As alternatives to PPIs, misoprostol and H2RAs can be used in the prevention of NSAID related ulcers and their complications, and their use is cost effective
- ➢ PPU co-therapy is effective in the healing and prevention of recurrence of ulcers in patients maintained on long-term NSAID therapy

Adapted from Arora et al. Clinical Gastroenterol and Hepatology 2009; 7: 725-735.

It is now recognized that NSAIDs and coxibs may damage the upper and the lower GI tract. They both also carry risk for cardiovascular damage, such as myocardial infarction and stroke. Therefore, the risk stratification must be in two dimensions, the GI as well as the cardiovascular systems. Carefully consider the need for gastroprotection in every NSAID user over the age of 65 years. The situation is even more complex, considering the need for some persons to be on anticoagulants or antiplatelet agents. Furthermore, it has been suggested that some PPI's interfere with the therapeutic benefit of clopidogrel. In patients with eradicated H.pylori but still on ASA/NSAIDs, standard dose PPIs (all agents have similar efficacy) are effective in reducing ulcer risk and in promoting healing. In H.pylori negative patients who have a history of ulcer bleeding on low-dose ASA alone, the combination of low-dose ASA and a PPI is associated with a lower risk of recurrence of ulcer complications at 1 year as compared to clopidogrel (an antiplatelet agaent) alone.

4. Choices During Pregnancy and Lactation

Some women of reproductive potential, may try to manage their dyspeptic symptoms with nonprescription antacids, barrier agents, H2RAs and PPIs. These medications are considered to be generally safe to use during pregnancy and lactation, (FDA pregnancy class B, except for oneprazole which is class C) with the caveat that the symptoms are from a condition in the upper GI tract and not from other pregnancy associated conditions (e.g. constipation, cholelithiasis, urinary tract infection or hypertension). If a diagnostic test for H.pylori (serology, endoscopy, UBT[with the ^{13}C isotope]) were done during pregnancy or lactation, treatment for the *H. pylori* infection should be postponed until after pregnancy and lactation. There is no need to test the infant for H.pylori if the mother is infected.

5. Proton Pump Inhibitors (PPIs)

The PPIs are generally considered to be a very safe class of medications. The few suggested associations of long-term use of PPIs and complications is given in Table 22 and 23. Retrospective epidemiological studies detail an association between the use of PPIs and an increased risk of hip fractures, and raise the possibility that this risk is increased with the dose and duration of PPI. There are numerous factors for the development of osteoporosis, and when these were taken into account in

a Canadian cross-sectional study and appropriate consideration of confounding variables were taken into account, PPIs did not add to the risk of osteoporosis (Targownik et al., 2010).

The antiplatelet function of clopidogrel may be modestly reduced by PPIs, but there is no difference in cardiovascular outcome in those who do, or don't use PPIs (*Lancet* 2009).

Table 22. PPIs are associated with alterations in gastric histology in *H. pylori* negative and positive persons

- ➢ *H. pylori* negative persons
  - o Older persons have an increased risk of moderately severe gastritis.
  - o PPIs may improve (and certainly do not worsen) pre-existing gastritis
  - o PPIs do not cause atrophic gastritis

- ➢ *H. pylori* positive persons
  - o *H. pylori* causes antral or body acute or chronic gastritis, atrophy and metaplasia
  - o *H. pylori*- associated chronic gastritis may progress (to gastric atrophy, intestinal metaplasia, and gastric cancer)
  - o *H. pylori* plus PPIs may cause progression or acceleration from gastric antrum-predominant chronic gastritis, to body-predominant chronic gastritis
  - o *H. pylori* eradication probably causes regression of gastric atrophy or intestinal metaplasia
  - o Gastric body-predominant atrophic gastritis is a risk factor for gastric cancer

(Thomson et al, 2009)

Table 23. PPIs change the bioavailability or metabolism of some drugs

- o PPIs reduce gastric acid, and thereby reduce the bioavailability of drugs requiring intragastric acidity to maximize their absorption and bioavailability (ketoconazole, itraconazole, indinpuir).
- o PPIs alter the hepatic clearance of some drugs.
- o PPIs may show a rare class action effect on Vitamin K antagonist.
- o PPIs may differ on their possibility of causing drug interactions.

(Thomson et al, 2009)

Table 24. The importance of physiological hypergastrinemia associated with the use of PPIs

- o PPIs modestly increase serum gastrin concentration in persons who are *H. pylori* negative or positive
- o *H. pylori* infection, even without use of PPIs, inceases serum gastrin concentration
- o PPIs do not increase risk of gastric or esophageal cancer, but increases apoptosis
- o PPIs increase ECL cell numbers, and possibly also increase linear or micronodular hyperplasia, but the different PPIs have varying effects in causing physiological hypergastrinemia
  - Lansoprazole > Omeprazole > Pantoprazole

(Thomson et al, 2009)

The long-term use of PPIs is suspected but has not been convincingly proven to cause or accelerate the progression of pre-existing chronic gastritis, corpus gastric atrophy or intestinal metaplasia. The long-term use of PPIs has not been convincingly proven to cause ECL cell hyperplasia or carcinoid tumors. PPI use is associated with parietal cell hyperplasia and up to 4-fold increased incidence of fundic gland polyps (FGP). FGP also occur in the presence of *H. pylori* infection, and eradication of *H. pylori* or stopping long-term use of PPIs is associated with regression of FGP. Sporadic FGP is rarely associated with dysplasia, but never gastric adenocarcinoma, up to date. Dysplasia may occur in 25-44% of gastric polyps in persons with familial adenomatous polyposis. PPI use is associated with the development of fundic gland polyps (FGP). FGP occur in the presence of *H. pylori* infection. Eradication of *H. pylori* or stopping PPI is associated with regression of FGP. FGP may occasionally become dysplastic, but almost exclusively in persons with familial adenomatous polyposis.

PPIs may mask symptoms or heal early gastric cancer, but there is no data on survival. PPIs are not associated with an increased risk of latent iron deficiency, or iron deficiency. In elderly patients who may already have gastric atrophy (possibly from *H. pylori* infection), PPIs used long-term may reduce serum vitamin B12 concentrations.
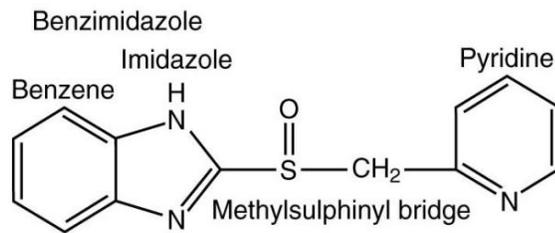
Figure 13. Structure of proton pump inhibitors (PPIs).
   o PPIs consist of two heterocyclic moieties, a benzimidazole ring, and a pyridine, connected by a methylsulphinyl bridge. PPIs are weak bases (pKa 4-5) that accumulate and activate in acidic spaces within the body that have a pH less than 4.
   o Once activated within the parietal cell canaliculus, the PPI binds covalently with certain cysteine residues within the α-subunit of the inserted H^+,K^+-ATPase.

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-14, pg 824, Ninth Edition, 2010.
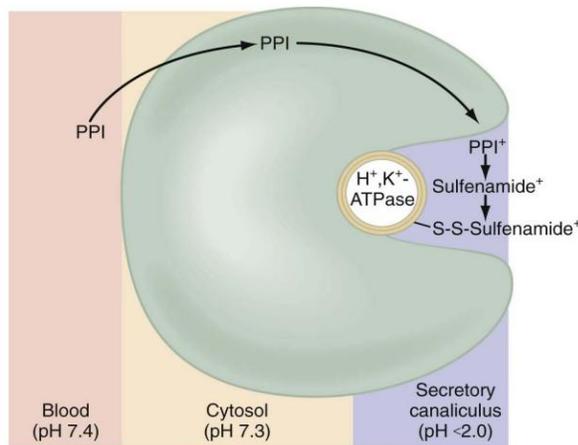
Figure 14. Model illustrating the mechanism of action of proton pump inhibitors (PPIs).
- o PPIs reach the parietal cell from the bloodstream, diffuse through the cytoplasm, and accumulate in the acid environment of the secretory canaliculus.
- o In the canaliculus, the PPI becomes protonated and trapped as a sulfenic acid followed by conversion to a sulfenamide.
- o The sulfenamide binds covalently by disulfide bonds to one or more cysteines of the H^+,K^+-ATPase to inhibit the enzyme.
- o Whereas all PPIs bind to cysteine 813, omeprazole also binds to cysteine 892, lansoprazole to cysteine 321, and pantoprazole to cysteine 822.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-15, pg 825, Ninth Edition, 2010.

6. Upper GI Bleeding

Upper GI bleeding is a common and potentially fatal condition of dudodenal and gastric ulcers.Bleeding peptic ulcers need to be distinguished from bleeding esophageal varices, secondary to portal hypertension. Even in the patient with known cirrhosis, UGIB is still usually due to peptic ulcer disease.

6.1 Goals of GI therapy

The goals of therapy in the patient with UGIB include: (ABCs) to resuscitate and save the patient's life and to prevent hypoxia-related damage to other organs; to make a diagnosis, to heal the underlying lesion; to perform ENT where appropriate; and to prevent recurrences. The distribution of the endoscopic type of bleeding ulcers is clean-based, 55%; a flat pigmented spot, 16%; a clot, 8%; and active bleeding, 12% (Enestvedt BK et al, 2008:422-9).

Other common sources of bleeding include erosive gastroduodenitis, esophagitis, Mallory-Weiss tears, angiodysplasia, Dieulafoy lesions and neoplasia. In most cases, bleeding stops spontaneously. However a minority rebleeds or continues to bleed despite attempts at hemostasis. This subpopulation accounts for most of the morbidity, mortality and resource

consumption associated with upper gastrointestinal hemorrhage. Risk stratification allows targeted application of medical, endoscopic and surgical therapy. Despite remarkable advances in each of these domains, however, approximately 1 in 20 patients who present with upper gastrointestinal bleeding will die over the course of their hospitalization. When the patient vomits coffee ground-appearing blood or fresh red blood, the bleeding arises from the upper GI tract, proximal to the ligament of treitz. The passage per rectum of black stools containing blood (melena) arises from relatively slow bleeding of small amounts of blood from the upper GI tract, small intestine, or from the right side of the colon. If the patient passes fresh red blood per rectum, they may be rapidly losing large amounts of blood from the upper GI tract, or more slowly losing smaller amounts of blood from the lower GI tract.

When the patient presents with an UGIB, clinical risk stratification is performed. If the patient is high risk then prompt endoscopy is performed to further stratify the risk from the endoscopic appearance of the bleeding lesion.

A negative NG aspirate in the patient who presents with melanoma or hematoschezia reduces the likelihood of an upper GI source of the bleeding, but because of curling of the tube or duodenal bleeding which does not reflux into the stomach, 15-18% of persons with an upper GI source for bleeding will have a non-bloody aspirate.

6.2. Presentation and Risk Stratification

Bleeding from the upper gastrointestinal tract (proximal to the ligament of Treitz) manifests typically with overt hematemesis or coffee ground emesis, or with passage of melena per rectum. Brisk hemorrhage with rapid transit can present with maroon stool, hematochezia or features of hemodynamic instability. In all cases, the priority at initial assessment is to ensure hemodynamic stability and initiate appropriate volume resuscitation before conducting a detailed history and physical examination.

Key features of the history include: symptoms of hemodynamic instability (such as presyncope); prior upper gastrointestinal and liver disease with or without hemorrhage; other blood loss suggestive of an underlying bleed- ing diathesis; use of medications known to cause gastrointestinal injury (such as aspirin and NSAIDs); alcohol consumption; and family history of gastrointestinal pathology. On physical examination, key features include serial assessment of postural vital signs, thorough examination of the abdomen, careful inspection of the skin and mucus membranes for telangiectasia, assessment for the stigmata of chronic liver disease, and digital rectal examination. A rapid estimate of blood loss can be made at the bedside: 50% loss of blood volume is suggested by systolic blood pressure < 100 mm Hg, a pulse rate > 100 BPM and a Hgb < 100 g/L In all cases of overt hemorrhage, care must be taken to exclude respiratory or nasopharyngeal sources of blood loss. Passage of a nasogastric tube for aspirate can be informative; a biliary aspirate suggests a source of bleeding distal to the ampulla of Vater, while a bloody aspirate suggests a high-risk lesion and increased risk of mortality.

An upper GI series (e.g., barium swallow) must not be performed in the patient with UGIB. The diagnostic accuracy is poor in this setting, it may obscure a clear field for subsequent esophagogastroduodenoscopy, and endoscopic hemostatic therapy (EHT) cannot be performed if the field of vision is obscured by barium. All patients with UGIB should be referred for Esophagogastroduodenoscopy (EGD) after they are stabilized. The timing will depend on the suspected severity of bleeding, the likely cause and the patient's general

condition, but ideally should be done within 12–24 hours of the presentation of the patient.[6] Prompt EGD will identify the lesion in about 90% of patients. The most common EGD finding is a peptic ulcer or erosions. Inability to make a diagnosis is usually due to profuse bleeding.

Table 25. A simple clinical method to estimate volume depletion

	Class I	Class II	Class III	Class IV
➢ Blood loss (mL)	<750	750-1000	1500-2000	>2000
➢ Blood loss (% blood volume)	<15	15-30	30-40	>40
➢ Heart (beats/min)	<100	>100	>120	>140
➢ Blood pressure	Normal	Normal	Decreased	Decreased
➢ Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
➢ Ventilatory rate (breaths/min)	14-20	20-30	30-40	>35
➢ Urine output (mL/hr)	>30	20-30	5-15	Negligible
➢ Mental status	Slightly anxious	Midly enxious	Anxious and confused	Confused and lethargic
➢ Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Printed with permission: Atkinson RJ and Hurlston DP. *Best Practice & Research Clinical Gastroenterology* 2008; 22: pg 234.

Prognosis may be established at the time of EGD. A patient with a clean-based ulcer who is stable, reliable, otherwise healthy and who has family support and transportation available may be discharged home from the emergency room after endoscopy. Obtain two biopsies for *H. pylori* from the gastric antrum. Obtain two additional biopsies for *H. pylori* from the gastric body in patients who have recently been on acid suppression therapy.

Figure 15. Angiodysplasias
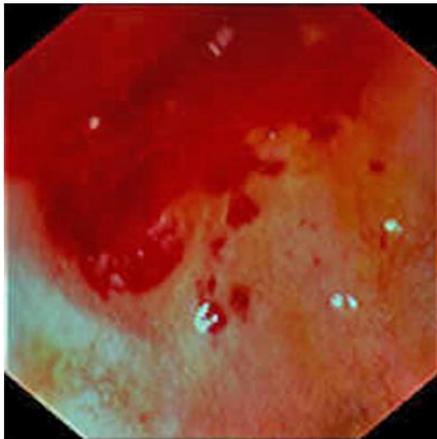
Figure 16. Upper GI bleed

Figure 17. Upper GI bleed
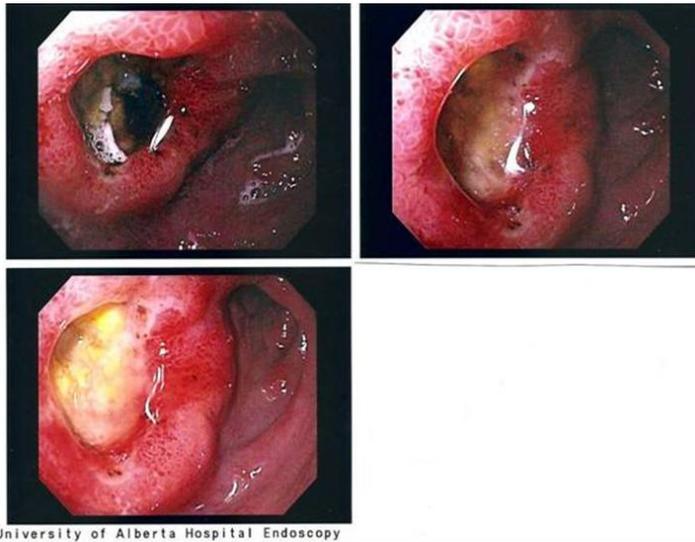
University of Alberta Hospital Endoscopy

Figure 18. Ulcer, possibly *H. pylori* associated

Upper gastrointestinal endoscopy (ideally within 24 hours of presentation) is a key component of patient assessment, and is often essential to diagnosis, prognosis and treatment. In most cases, an experienced endoscopist can localize the source of bleeding and estimate the risk of rebleeding. Of note, the Forrest classification of peptic ulcer stigmata (first reported in 1974) has withstood the test of time as a powerful predictor of the risk of rebleeding (Table 26). By combining clinical and endoscopic criteria, clinicians can estimate risk with even greater accuracy. The Rockall score combines five domains (age, comorbidity, hemodynamic stability, bleeding source and Forrest classification) to predict rebleeding and mortality. Patients at low risk can be discharged home from the emer- gency department for outpatient follow-up.

Table 26. The rates (%) of rebleeding, surgery and mortality, without and with endoscopic hemostatic therapy (ET), using the Forrest classification of bleeding peptic ulcers

Forrest Classification: EGD appearance	Prevalence	Rebleeding Rate (%)		Surgery Rate (%)		Mortality rate (%)	
		No ET	ET (~70%↓)	No ET	ET (~80%↓)	No ET	ET (~50%↓)
➢ Active Bleeding (Ib, ouzing)*	18	55	20	35	7	11	<5
➢ Visible vessel (IIa); not bleeding	17	43	15	34	6	11	<5
➢ Adherent clot (IIb)	15	22	5	10	2	7	<3
➢ Flat pigmented spot (IIc)	15	10	<1	6	<1	3	<1
➢ Clean ulcer base (III)	35	<5	<1	<1	<1	<1	<1

*Forrest 1a, active bleeding (spurting)

Abbreviation: ET, endoscopic hemostatic therapy
Printed with permission: Atkinson RJ and Hurlstone DP. *Best Practice & Research Clinical Gastroenterology* 2008; 22(2): page 235.

Gastric and duodenal ulcers are the most common lesions in Canadian patients with nonvariceal UGIB. After EHT, the early rates of rebleeding, surgery and mortality are respectively reported to be 14.1%, 6.5% and 5.4%.[13] In the GI bleed patient, the short-term mortality may be increased by co-morbid conditions such as diabetes[14], and in the elderly[15] where 30-day mortality in octogenarians may exceed 40%.[16] Post interventional complications[17] and hypoalbuminemia[18] may also add to the mortality.

In bleeding esophageal varices, endoscopic variceal band ligation or sclerotherapy is highly effective in stopping bleeding and preventing rebleeding. Band ligation is preferred because there are fewer complications. For bleeding gastric varices, the tissue adhesive cyanoacrylate may be carefully applied. Endoscopic triage provides for assessment of the risk of the UGIB.[8] In the more serious lesions seen in EGD, such as an ulcer with an adherent clot, visible vessel or active bleeding, EHT must be used. EHT involves coaptive thermal

coagulation, injection of a large volume (30ml) of epinephrine and saline, or a sclerosing agent and/or a mechanical technique (banding, hemoclip, staples, sutures). In nonvariceal bleeding, a combination of injection (e.g., epinephrine), thermal or mechanical therapies should be used.

Table 27. Similarities and differences in the clinical features of NVUGIB in elderly versus younger persons

➢ Similarities
  o Presenting manifestations of bleedings: hematemesis (50%); melena (30%); hematemesis and melena (20%)
  o Peptic ulcer disease most common etiology
  o Safety and efficacy of endoscopic therapy

➢ Differences (in elderly patients)
  o ↓ Antecedent symptoms (abdominal pain, dyspepsia, heartburn)
  o ↑Prior aspirin and NSAID use
  o ↑ Presence of comorbid conditions
  o ↑ Hospitalization, rebleeding, death

Abbreviation: NVUGIB, non-variceal upper GI bleeding

Printed with permission: Yachimski PS and Friedman LS. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(2): page 81.

In the patient with UGIB due to esophageal varices (5-30% of all cases of UGIB), adding octreotide plus infusion for 2-5 days for EHT improves the control of bleeding. Also, adding ceftriaxone or quinolones reduces bacterial infection and mortality (DeFranchis, 2005). Recurrent esophageal variceal bleeding in the Child-Pugh class A or B cirrhotic, which occurs despite repeated endoscopic variceal banding or maintenance use of nonselective beta blocker may require the placement of TIPS (83% vs 11%, likely due to the TIPS shunt stenosis), with no difference in rebleeding, hepatic encephalopathy or death (Henderson et al., 2006). Gastric varices due to splenic vein thrombosis can be cured by splenectomy.

Endoscopic hemostatic therapy has been shown to reduce rebleeding, surgery and death among patients with high-risk endoscopic stigmata (Forrest classi- fication Ia, Ib or IIa). Both injection therapy (saline +/- 10,000 epinephrine) and thermal coagulation therapy to ablate the bleeding vessel are effective. The combination of injection therapy plus thermal coagulation therapy is more effective than either intervention alone. In patients with adherent clots (Forrest classification IIb), management is controversial.

Aggressive irrigation to dislodge the clot and treatment of the underlying lesion is generally accepted. Clinical trials from expert centres have shown better outcomes when a cold snare is used to remove the clot, but many clinicians are reluctant to use this technique for fear of precipitating a brisk bleed. The use of endoscopic clips for hemostasis is a promising technique undergoing assessment in clinical trials.

For high risk lesions (active bleeding, visible vessel, adherent clot), endoscopic hemostatic therapy is performed, with good results for the reduction in the risk of rebleeding, need for surgery, and death. Note the very high rate of these complications. The patient-related

adverse prognostic variables are not meant to predict the patient with these high risks, before EGH is performed. In the patient with high risk of lesions treated by EHT, the EHT is followed by 3 days of IV PPIs, and then switched to oral PPIs. For low risk lesions, the patient is started directly on oral once-a-day PPI.

Acid suppression can improve clot stability and platelet aggregation. Accordingly, medical therapy of non-variceal upper gastrointestinal hemorrhage is focused on achieving sustained and substantive elevation of gastric pH. Clinical trials of intravenous histamine-2-receptor antagonists have been disappointing, in part due to early induction of pharmacologic tolerance. However, an intravenous bolus of omeprazole followed by an intravenous infusion for 72 hours has been shown in several well-designed clinical trials to reduce the risk of rebleeding after endoscopy in patients with high-risk endoscopic lesions (Forrest classification Ia, Ib and IIa). Meta-analyses pooling these trials have also shown intravenous proton pump inhibitors to be associated with significant reductions in surgery and mortality. RCTs show that adding bolus plus infusion of PPI to endoscopic hemostatic therapy (EHT) significantly decreased bleeding (NNT, 12) surgery (NNT, 28) and death (NNT, 45) (Laine L, et al. Clin Gastroenterol Hepatol 2009: 33-47). In the ICU patient on a mechanical ventilator, IV H2-receptor blocker or PPI through the nasogastric tube is superior to sucralfate to reduce stress when bleeding (Cook DJ, et al. The New England Journal of Medicine1998: 791-7; Conrad SA et al. Crit Care Med 2005; 33: 760-5).

Several controversies persist in the medical management of non-variceal upper gastrointestinal hemorrhage. First, the empiric use of proton pump inhibitors in patients prior to endoscopy has intuitive appeal but has not been tested in clinical trials. High doses of oral proton pump inhibitors may also be effective, but no rigorous head-to-head comparison with intravenous dosing has assessed clinical outcomes. Intravenous infusion of somatostatin analogs such as octreotide may also reduce rebleeding, and may be use- ful in patients with significant bleeding facing delays to endoscopy. Other agents such as tranexamic acid and recombinant factor VII can be considered in refractory patients, but have not been tested in clinical trials.

For patients who rebleed after an initial attempt at endoscopic hemostasis, repeat endoscopy to reassess the lesion and apply further endoscopic treat- ment as needed is appropriate. However, routine second-look endoscopy in patients with no evidence of recurrent bleeding is not advocated.

Table 28. Patient-related adverse prognostic variables which may be used for risk stratification in persons with acute NVUGIB

- Increasing age
- Red blood in the emesis or stool
- Increasing number of comorbid conditions (especially renal failure, liver failure, heart failure, cardiovascular disease, disseminated malignancy)
- Shock – hypotension, tachycardia, tachypnea, oliguria on presentation
- Increasing number of units of blood transfused
- Onset of bleeding in the hospital
- Need for emergency surgery
- Use of anticoagulants, glucocorticosteroids

Abbreviations: NVUGIB, non-variceal upper GI bleeding ; UGIB, upper GI bleeding

Table 29. Factors to consider when performing EGD in pregnant women

- A strong indication is always needed, particularly in high-risk pregnancies
- Whenever possible, endoscopy should be deferred until the second trimester
- The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)
- Procedure time should be short
- To avoid inferior venal cava or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
- Presence of fetal heart sounds should be confirmed before sedation and after the procedure
- Obstetric support should be immediately available
- No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)

Printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 435.

NVUGIB may occur during pregnancy, and the management is the same: stabilize, EGD, EHT, depending upon the cause of the bleeding, followed by IV or po PPIs. There are special factors to consider when performing EGD in pregnant women (Table 29). Also, there are similarities and differeces to consider in the clinical features of NVUGIB in elderly (>65 years) versus younger persons (Table 28).

In some persons who present with upper/lower GI bleeding, or chronic iron deficiency anemia, they have no diagnosis after carefully performed EGD/colonoscopy. They are considered to suffer from obscure GI bleeding, and there are numerous diagnostic methods which may be used to determine the cause of this obscure bleeding (Table 30).

6.3. Surgery

Between 5% and 10% of patients who present with acute upper gastrointestinal bleeding will require surgery because of continued or recurrent hemorrhage. Although this proportion is gradually declining, it remains substantial as improvements in medical and endoscopic therapies are offset by the increasing age and comorbidity of patients admitted with gastrointestinal bleeding. The decision to perform surgery must be individualized, but consider factors such as patient comorbidity, transfusion requirements, the nature of the bleeding lesion and the anticipated success of further endoscopic therapy. Surgery should be considered early in patients at high risk of complications such as perforation (e.g., large, deep anterior duodenal ulcers).
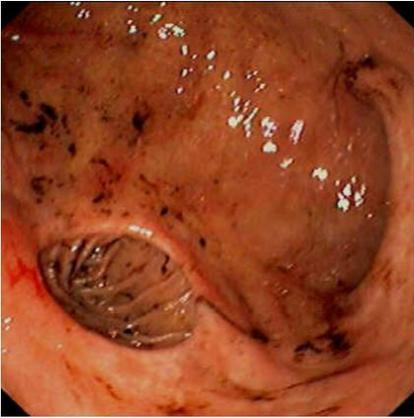
Figure 19. Gastrojejunostomy

Gastric Surgery may be performed in the setting of the patient with an Upper GI bleed, gastric cancer, and for weight reduction. Obesity will be discussed in the chapter on nutrition, but it is useful to consider bariatric surgery here within the contest of the rate of common complications arising from gastric surgery performed for any reason.
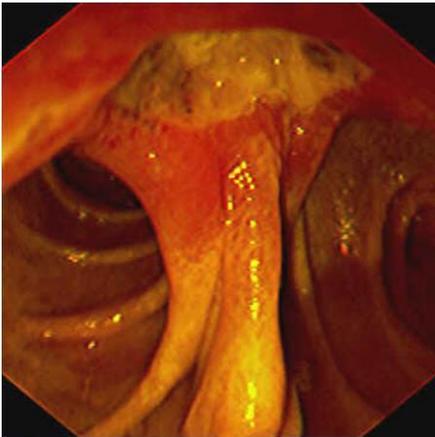
Figure 20. Gastric Anastomotic Ulcer

Table 30a. Bariatric procedures

➢Specific procedures
  o Gastric bypass (Roux-en-Y)
    – Anastomotic leak with peritonitis
    – Stomal stenosis
    – Marginal ulcers (ischemia)
    – Staple line disruption
    – Internal and incisional hernias
    – Nutrient deficiencies (usually iron, calcium, folic acid, vitamin B12)
    – Dumping syndrome

- o Gastroplasty
  - – GERD
  - – Stomal stenosis
  - – Staple line disruption
  - – Band erosion
- o Gastric banding
  - – Band slippage
  - – Erosion
  - – Esophageal dilation
  - – Band infections
- o Biliopancreatic diversion
  - – Anastomotic leak with peritonitis
  - – Protein-energy malnutrition
  - – Vitamin and mineral deficiencies
  - – Dehydration

Table 30b. Complications for each bariatric procedure, and complications common to all bariatric surgical procedures

➢Complications common to all bariatric surgical procedures
- o CNS
  - – Psychiatric disturbance
- o Lung
  - – Atelectasis and pneumonia
  - – Deep vein thrombosis
  - – Pulmonary embolism
- o CVS
- o GI
  - – Anemia
  - – Diarrhea
  - – Ulceration
  - – GI bleeding
  - – Stenosis
  - – Gallstones
- o Metabolic
  - – Bone disease
  - – Too rapid weight loss
- o Surgical
  - – Wound infection
  - – Failure to lose weight
  - – Mortality (0.5-1%)

Abbreviation: CNS, central nervous system

Adapted from: Klein S. *2006 AGA Institute Post Graduate Course*: page 175.

The three most common bariatric surgical procedures include adjustable gastric bands (AGB), sleeve gastrectomy (SG), and roux-en-Y gastric bypass (GBP). Laparoscopic AGB provided less of more than 50% of excess weight in 84% of adolescents with a BMI > 35, as compared with 12% in a lifestyle group (O'Brien et al. 2010). The improvement in T2DM is more frequent with gastric bypass than banding, with rapid normalization of glucose metabolism (decrease in insulin resistance and increase in insulin secretion) occurring even before weight loss (Laville and Disse 2009). There may even be a decline in diabetes-associated death. Natural Orifice Transluminal Endoscopic Surgery (NOTES), endoscopy and endoluminal surgery are being developed as surgical bariatric procedures (Tsesmeli and Coumaros 2010). GBP appears to be the superior procedure, and weight loss may be just as much due to changes in gastrointestinal hormones as to restriction or malabsorption (Bueter et al. 2010). Unfortunately, these procedures are associated with multiple complications (Table 31a&b). It is a useful exercise to consider the mechanisms responsible for the nutrient deficiencies which may develop after bariatric surgery, let alone any type of gastric surgery which may be used for example for peptic ulcer disease or for gastric malignancy (Table 32).

Table 31. Mechanisms or causes of iron- and B12-deficiency associated anemia, diarrhea, metabolic bone disease, and recurrent gastric ulceration in a patient having had a Billroth II partial gastrectomy for peptic ulcer disease (PUD), gastric cancer (GCA) or morbid obesity (bariatric surgery) and Roux-en-Y

➤Iron
- Pre-surgery iron deficiency
- Decreased intake from post-op symptoms (anorexia, early satiety)
- Decreased acid leads to decreased pepsin and decreased meat (iron) digestion
- Decreased acid: inhibits the acid-mediated solubilizing and reducing of inorganic dietary iron (Fe^{3+} .[ferric] .. Fe^{2+})ferrous])
- Decreased absorption of Fe^{2+}, Ca^{2+}, BII, bypassing site of maximal absorption
- Can be slow bleeding at surgical site
- Bile gastritis
- Gastric stump cancer

➤B12
- Pre-surgery deficiency
- Decreased intake
- Loss of stimulated co-ordinated release of pancreatic "R" factor
- Decreased intrinsic factor
- Loss of HCl/pepsinogen to liberate food B12
- Bacterial overgrowth syndrome

➤Diarrhea
- Magnesium-containing antacids, PPI's
- Dumping
- Retained antrum ($\uparrow$ gastrin)
- Hypergastrinemia, HCL hypersecretion ($\uparrow$ volume, mucosal damage)
- Bypassed duodenum
- Unmasked celiac disease
- Unmasked lactose intolerance

- o Unmasked bile acid wastage
- o Primary or secondary (unmasked) pancreatic insufficiency
- o Bacterial overgrowth syndrome (BOS)
- ➢ Metabolic bone disease
  - o Pre-existing osteoporosis ↓ Ca^{2+} solubilization
  - o ↓ vitamin D or Ca^{2+} intake
  - o Bypass of site of maximal absorption of Ca^{2+} (duodenum)
  - o Binding Ca^{+2} (unabsorbed fatty acids)
- ➢Peptic ulceration (previous peptic ulcer disease [PUD])
  - o ↑ gastrin – ZES, incomplete vagotomy, gastric retention, afferent loop syndrome
  - o *H. pylori* infection
  - o NSAIDs, ASA use
  - o "Stump" Cancer
  - o Ischemia at anastomosis
  - o Bile gastritis
- ➢ Presentations of ZES (Zollinger Ellison Syndrome)
  - o PUD – severe, multiple, unusual sites; GERD-like symptoms
  - o Diarrhea
  - o Recurrent ulceration (with or without gastric surgery)
  - o Associated MEN I syndrome
  - o Thick gastric folds

Abbreviations: BOM, bacterial overgrowth syndrome; GCa, gastric cancer; MEN, multiple endocrine neoplasia ; PPIs, proton pump inhibitor; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

6.4. Obscure GI Bleeding

Understandably, at the time of active bleeding from the upper or lower GI tract, endoscopic visualization of the site and cause of bleeding may be obscured by the presence of blood. Even when EGD and colonoscopy are performed again under ideal circumstances, the cause of bleeding may be obscure. In those persons with recurrent episodes of bleeding or with unexplained iron deficiency anemia, further diagnostic methods may need to be used (Table 33), and particularly small bowel lesions such as vascular abnormalities, polyps, or ulcers may be the culprit.

Table 32. Diagnostic methods for determining the cause of obscure GI bleeding

- ➢ Endoscopy
  - o Capsule endoscopy (CE)
  - o Double balloon enteroscopy (DBE)
  - o Push enteroscopy (PE)
  - o Intraoperative endoscopy
  - o Esophagogastroduodenoscopy (EGD)
  - o Colonoscopy
- ➢ Small bowel contrast X-ray
  - o Small bowel single contrast
  - o Small bowel double contrast (enteroclysis)

139

- CT/MRI
  - CT angiography
  - CT/MRI enteroscopy
  - CT-enterocylsis
- Angiography
  - Elective (no acute bleeding)
  - With acute bleeding
- Scintigraphy
  - Erythrocyte scintigraphy (RBC scan)
  - Meckel's scintigraphy
- Video capsule endoscopy

Adapted from: Heil U. and Jung M. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): page 402.

6.5. Conclusions

Appropriate management of acute upper gastrointestinal hemorrhage entails early resuscitation and triage, careful clinical assessment, early endoscopy, intravenous proton pump inhibitors infusion (if indicated) and access to a skilled surgical team. Given the high prevalence of upper gastrointestinal bleeding, each acute care hospital and health care system should develop institution-specific protocols for its management. These protocols should address aspects of triage and multidisciplinary care including access to a therapeutic endoscopist skilled in endoscopic hemostasis and trained support to assist with urgent endoscopy. Despite remarkable advances in medical and endoscopic therapy, non-variceal upper gastrointestinal hemorrhage continues to impose a significant disease burden.
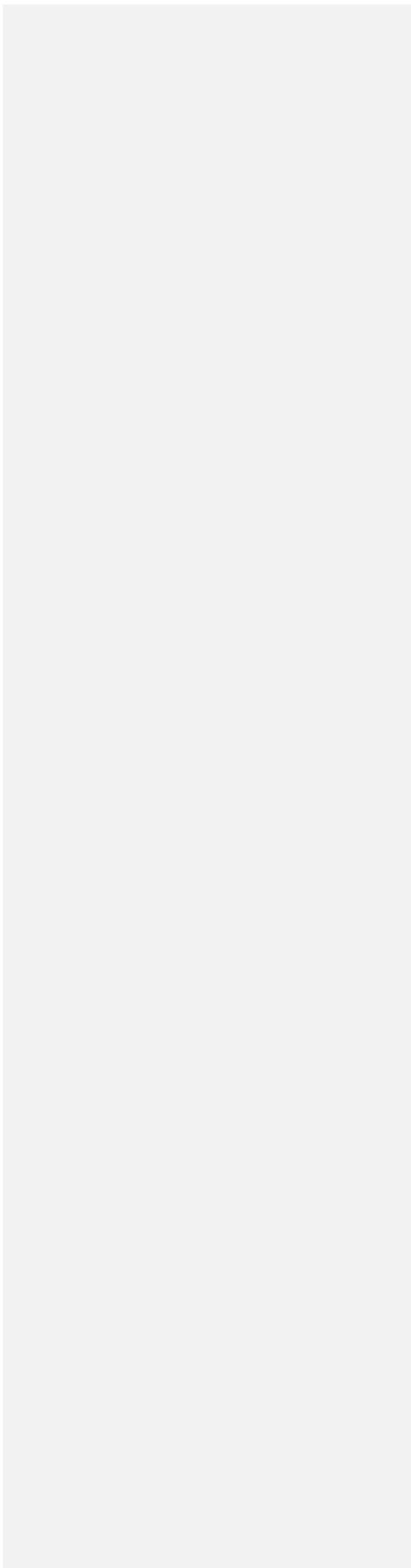
Chapter 5: Gastritis and Gastric Neoplasia

A.B.R. Thomson and R.H. Hunt

1. Gastritis

1.1. Introduction

The term "gastritis" has been used variously and incorrectly to describe symptoms referable to the upper gastrointestinal tract, the macroscopic appearances of inflammation or injury in the stomach at endoscopy and the histologic features of inflam- mation or injury to the gastric mucosa at microscopy. Unfortunately, there is a very poor correlation between an individual's symptoms and any abnormalities evident at endoscopy or microscopy. Upper gastrointestinal tract symptoms are best considered under the term "dyspepsia," while endoscopic features such as erythema, hypertrophy, friability, petechial hemorrhages and erosions should be described as such and correlated with the histological features of inflammation and damage. Only the histological features compatible with inflammation may be correctly used with the term gastritis, which will be the subject of the present chapter (Table 1).

Gastritis is defined as inflammation of the gastric mucosa (Figure 1), and the use of the term should therefore be based solely on an examination of gas- tric mucosal biopsies. Gastric mucosal biopsies should be obtained if there is endoscopic evidence of any mucosal abnormality, including erosions, ulcers, thickened folds, polyps or masses, or if there is a suspicion of *H. pylori* infection (Figure 2) or damage due to the ingestion of NSAIDs. Indeed, it has been proposed that an endoscopy performed without mucosal biopsies is an incomplete examination. In addition to specific lesions or abnormalities, biopsies should also be taken from the antrum (2 biopsies) and body of the stomach (2 biopsies) and some authors also recommend a fifth biopsy from the gastric angulus or incisura to identify possible *H. pylori* infection in patients who have recently received acid suppression therapy.

Strictly, the term 'gastritis' should be used only to describe changes characterized by a mucosal infiltrate of inflammatory cells while changes attributable to the injurious effects of NSAIDs, alcohol and bile, for exam- ple, should be termed a chemical or reactive gastropathy. However, even a chemical gastropathy may be accompanied by inflammation and both entities will, therefore, be addressed.

Acute gastritis is characterized by an inflammatory infiltrate that is pre- dominantly neutrophilic and is usually transient in nature. Inflammation may be accompanied by mucosal hemorrhage and superficial mucosa sloughing and, when severe, acute erosive gastritis may be associated with gastrointestinal bleeding (Figure 3). Acute gastritis may cause epigastric pain, nausea and vomiting but it may also be completely asymptomatic.

Chronic gastritis is characterized by an infiltrate of lymphocytes, plasma cells, or both, that may also be associated with intestinal metaplasia and atro- phy of the epithelium. In intestinal metaplasia, the normal gastric epithelium is replaced by metaplastic columnar absorptive cells and goblet cells; these are usually small-intestinal in morphology although features of a colonic epithelium may be present. The development of atrophic gastritis and intesti- nal metaplasia is considered to be premalignant although the incidence of gastric cancer in gastric intestinal metaplasia is unknown and surveillance is not widely practised. In the Western world, histologic changes of chronic gas- tritis occur in up to 50% of the population in later life although the incidence of gastric cancer is falling, almost certainly due to the decreasing prevalence of *H. pylori* infection. Chronic gastritis rarely causes symptoms although it can be associated with nausea, vomiting and upper abdominal discomfort.

In addition to elements of chronicity, gastritis can also be categorized on the basis of identifiable etiology (e.g., infection, graft-versus-host disease, autoimmune, chemical gastropathy) or on the basis of histological appearance (e.g., granulomatous, eosinophilic, lymphocytic, hypertrophic) although, in practice, the categorization of gastritis may address both of these elements.

Gastritis is not itself often a cause of dyspepsia, unless there is *H. pylori*- or NSAID-associated peptic ulcer disease. Gastritis is a diagnosis made from the histological examination of gastric biopsies obtained on EGD. There are numerous causes of histologically diagnosed gastritis, and the importance of knowing the cause of the gastritis is to treat the underlying condition. It must be stressed that even when the cause of the gastritis is treated, such as in the person withy dyspepsia and a chronic *H. pylori* infection, curing the infection as well as the gastritis may have little benefit on the patient's dyspepsia (therapeutic gain only about 13%, versus 50% if there is *H. pylori* eradication in the person with *H. pylori* associated peptic ulcer disease).

1.2. Gastritides with Identifiable Etiology
1.2.1. Infectious Gastritides
1.2.1.1. Viral

Cytomegalovirus (CMV) infection of the gastrointestinal tract usually occurs in immunocompromised individuals. CMV gastritis may be associated with epigastric pain and fever and the gastric mucosa may be edematous and congested, with erosions or ulceration at endoscopy. The characteristic histo- logical finding is "owl-eye," intranuclear inclusions in cells of the mucosal epithelium, vascular endothelium and connective tissue.

Herpes infection with the H. simplex, H. varicella or H. zoster virus occurs by reactivation of a prior infection; again, this is seen most commonly in the immunocompromised patient, and leads to nausea, vomiting, fever, chills, fatigue and weight-loss. At endoscopy, the gastric mucosa has a cobblestone appearance due to multiple superficial linear ulcers and small raised ulcerated plaques, while histology shows numerous cells with ground-glass nuclei and eosinophilic, intranuclear inclusion bodies surrounded by halos.

Table 1. Causes of histologically-diagnosed gastritis.

- ➤ Drugs, chemicals, radiation
  - ○ Medications
    - – Asprin, NSAIDs, COXIBs
    - – Bisphosphonates, K^+ tablets
  - ○ Drugs, chemicals
    - – Alcohol, bile, cocaine, chemotherapy, radiotherapy, red peppers, pickles

- ➤ Infection
  - ○ Bacterial - *H. pylori*, Mycobacteria
  - ○ Viral-CMV, HSV
  - ○ Fungal
  - ○ Parasitic

- ➤ Graft-versus-host disease (GVHD)

- ➤ Autoimmune gastritis (pernicious anemia)

- ➢ Ischemia
  - o Atherosclerosis
  - o Sepsis
  - o Burns
  - o Shock
  - o Mechanical ventilation

- ➢ Associated with liver disease – GAVE, PHG

- ➢ Trauma/foreign body
  - o Nasogastric or gastrostomy tubes
  - o Bezoar
  - o Prolapse / sliding hiatal hernia/paraesophageal hernia
  - o Cameron ulcer (ulcer in hiatus hernia)

- ➢ Infiltration/ tumor
  - o Lymphocytic/ collagenous
  - o Granulomatous
  - o Eosinophilic
  - o Tumor

- ➢ Miscellaneous
  - o Gastritis cystica profunda
  - o Ménétrier's disease (hyperplastic,   hypersecretory gastropathy

Abbreviations: CMV, cytomegalovirus; GAVE, gastric antral vascular ectasia; GVHD, graft-versus-host disease; HSV,herpes simplex virus; PHG, portal hypertensive gastropathy

Adapted from: Lee EL, and Feldman M. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 1068; and printed with permission: Francis DL. *Mayo Clinic Gastroenterology and Hepatology Board Review*; 2008:67.

1.2.1.2. Bacterial

H. pylori is the most common gastric bacterial infection worldwide and, surprisingly, it remained almost unrecognized until the seminal work of Barry Marshall and Robin Warren (see previous chapter). The prevalence of *H. pylori* infection in the Western world is about 20-30% (25% in Canada) prevalence increases with age and, in the developing world, it may exceed 80%. *H. pylori* can be found in 90% of patients with chronic antral gastritis and most *H. pylori*-infected individuals have associated gastritis. Although many *H. pylori*-infected individuals have no symptoms, *H. pylori* is associated with an increased risk of developing peptic ulcer disease, gastric cancer and gastric 'MALT' lymphoma.

Although it initially causes antral gastritis, *H. pylori* may affect both antral and body-fundic mucosa. At endoscopy, the mucosa may appear coarse and reddened with thickened rugal folds but, with longer-standing infection, it may become thinned, flattened and atrophic. Chronic *H. pylori* gastritis is characterized by an infiltrate of lymphocytes and plasma cells in the lamina propria and lymphoid aggregates with germinal centres; a variable, active gastritis is characterized by neutrophils in the glandular and surface epithelial layer. *H. pylori* organisms

reside in the superficial mucous layer, over the mucosal surface, and in gastric pits; they can usually be seen with a standard hematoxylin and eosin stain but special stains, such as the Warthin-Starry silver stain, acridine orange fluorescent stain and Giemsa stain may be needed if organisms are sparse.

Over time, the initial antral-predominant gastritis progresses to a pangastri- tis and then to atrophic gastritis and intestinal metaplasia – precursors to the development of gastric cancer (the "Correa hypothesis"). Eradication of *H. pylori* infection usually with regimens comprising two antibiotics and an acid antisecretory agent, is associated with a decreased risk of peptic ulceration and its complications and, probably, with a decreased risk of gastric cancer and gastric MALT lymphoma.

Phlegmonous (suppurative) gastritis is a rare bacterial infection of the submucosa and muscularis propria and is associated with massive alcohol ingestion, upper respiratory tract infection, and immune compromise; it has a mortality rate in excess of 50%. At endoscopy, the mucosa may show granular, green-black exudates and, at histology, there is an intense polymorphonuclear infiltrate with gram-positive and gram-negative organisms. Emphysematous gastritis, due to Clostridium welchii, may lead to the formation of gas bubbles, along the gastric contour on x-ray. Treatment requires gastric resection or drainage and high-dose systemic antibiotics.

Mycobacterium tuberculosis gastritis is rare; ulcers, masses, or gastric outlet obstruction may be seen at endoscopy and biopsies show necrotizing granulomas with acid-fast bacilli. Mycobacterium avium complex gastritis is very rare, even in immunocompromised individuals; gastric mucosal biopsies show foamy histiocytes containing acid-fast bacilli.

Actinomycosis and syphilis are very rare causes of gastritis, although the incidence of gastric syphilis has increased in the US over the last two decades. In actinomycosis, endoscopy may reveal appearances suggestive of a gastric malignancy; biopsies show multiple abscesses containing Actinomyces israelii, a gram-positive filamentous anaerobic bacterium. In syphilis, endoscopy may show multiple serpiginous ulcers while biopsies show severe gastritis with a dense plasma cell infiltrate in the lamina propria, as well as some neutrophils and lymphocytes, gland destruction, vasculitis and granulomata.

1.2.1.3. Fungal and Parasitic

Candida and Histoplasma, the most common, albeit rare, fungal causes of gastritis are associated with impaired immune status; gastric phycomycosis (zygomycosis) is exceedingly rare but usually fatal. Parasitic causes of gastri- tis include Cryptosporidia, Strongyloides stercoralis, Anisakis (from raw marine fish), Ascaris lumbricoides and Necator americanus (hookworm).

1.2.2. Graft-Versus-Host Disease (Gvhd)

The stomach and esophagus are affected less often than small intestine and colon by GVHD, which usually follows allogeneic bone marrow transplanta- tion. Acute GVHD occurs between days 21 and 100 after transplantation and, if it affects only the stomach, it is associated with nausea, vomiting and upper abdominal pain. Endoscopic findings are non-specific and histology shows cell necrosis (apoptotic bodies — intraepithelial vacuoles containing karyorrhectic debris and fragments of cytoplasm) in the neck region of the gastric mucosa.

1.2.3. Autoimmune Gastritis

Autoimmune gastritis, comprising less than 10% of chronic gastritis cases, is caused by one or more autoantibodies to parietal cell components, including intrinsic factor and the acid-producing proton pump (H+,K+-ATPase). It is associated with other autoimmune disorders such as Hashimoto's thyroiditis and Addison's disease. Mucosal atrophy, with loss of parietal cells, leads to decreased production of acid and intrinsic factor; about 10% of these patients develop low serum vitamin B12 levels and pernicious anemia.
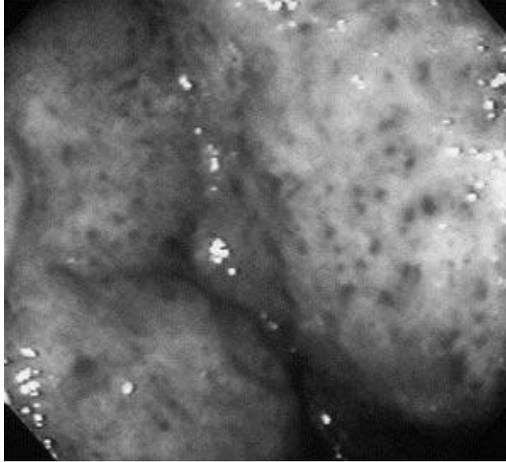
Figure 1. Fundal (Type A) gastritis
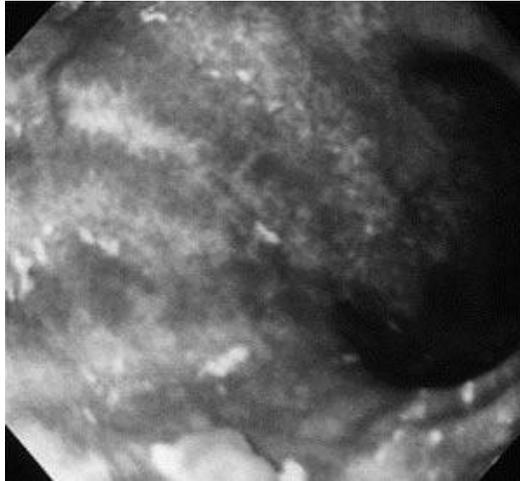
Figure 2. Chronic *H. pylori* gastritis
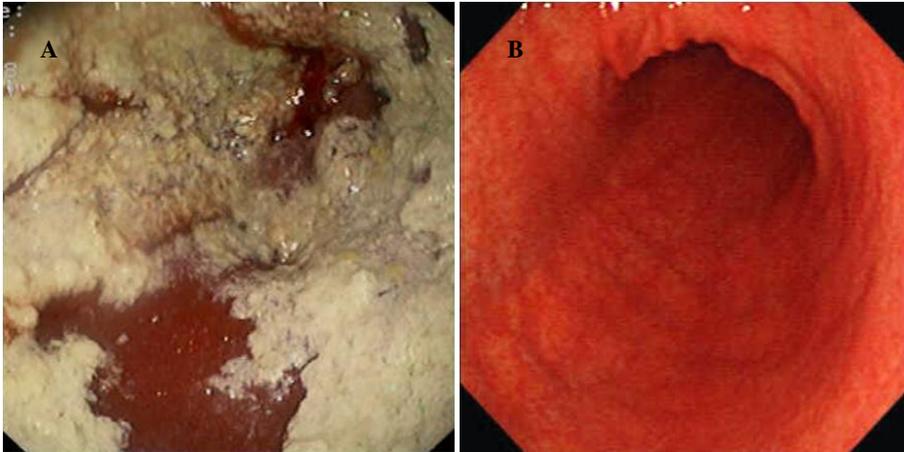
Figure 3. A) Candidiasis. B) Gastric atrophy

1.2.4. Chemical Gastropathy (Reactive Gastropathy)

  A number of different agents can produce gastric mucosal injury, characterized at endoscopy by hemorrhagic lesions and erosions (necrosis to the level of the muscularis mucosa) or ulcers (necrosis extending deeper than the muscularis mucosa). Biopsies show the typical changes of foveolar hyperplasia including an elongated, corkscrew appearance to the gastric pits, depletion of surface, mucin-containing cells, subepithelial hemorrhage and minimal inflammatory cell infiltrate.

  Aspirin (ASA) and other NSAIDs are the most common causes of a chemical gastropathy; cyclo-oxygenase-2 selective inhibitors (COX-2 or coxibs) are less likely to cause injury. While the patient's history of consuming NSAIDs is important to establish the diagnosis of NSAID-associated gastropathy, there are histological features which suggest the etiology. Bile reflux gastritis has become far less com- mon as partial gastrectomy (Billroth I and II) is now performed only rarely; however, bile gastritis also occurs after cholecystectomy or sphincteroplasty, or, occasionally, in the absence of prior surgery. Other causes of a chemical gastropathy include medications (e.g., potassium chloride supplements, bisphosphonates), alcohol, ischemia (chronic mesenteric insufficiency), cocaine, stress (in intensive care settings) and gastric bezoars. Portal hyper- tension produces a congestive gastropathy, with vascular ectasia but, again, only a minimal inflammatory infiltrate.
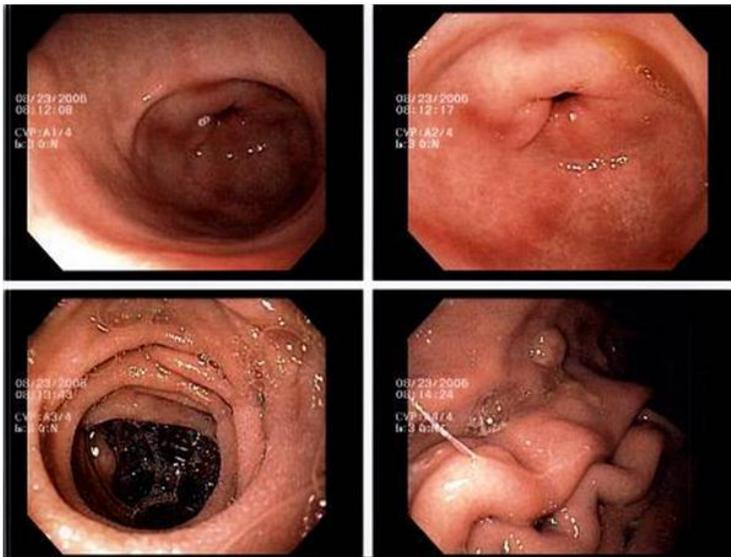
Figure 4. Thick gastric folds, gastric polyp

1.3. Gastritides Identified by Histological Appearance

1.3.1. Granulomatous Gastritides

Crohn disease is the most common cause of a granulomatous gastritis although the differential diagnosis includes sarcoidosis, foreign bodies, Churg-Strauss syndrome (granulomatous vasculitis), Whipple's disease, Langerhans cell histiocytosis (eosinophilic granuloma) and lymphoma.

Crohn disease of the stomach is uncommon, particularly in the absence of disease elsewhere in the gastrointestinal tract. Endoscopy may show mucosal reddening and nodules with or without overlying erosions and ulcers that may be elongated or serpiginous. Histological features include non-caseating granu- lomata, ulceration, chronic inflammation and submucosal fibrosis. Sarcoidosis of the stomach can be difficult to distinguish endoscopically and histologically from Crohn disease and the diagnosis must be based on the presence of other systemic features.

Xanthogranulomatous gastritis is characterized, histologically, by the presence of foamy histiocytes, inflammatory cells, multinucleated giant cells, and fibrosis and may extend into adjacent organs and simulate malignancy.

1.3.2. Gastritis with Specific Diagnostic Features

Collagenous gastritis has been reported in association with collagenous colitis and lymphocytic colitis; it is very rare. At endoscopy, non-specific findings include mucosal hemorrhages, erosions and nodularity while histology shows a chronic gastritis (plasma cells and intra-epithelial lymphocytes), focal atrophy and focal collagen deposition (20—75 m) in the lamina propria.

Lymphocytic gastritis is thought, by some, to be related to varioliform gas- tritis, which is associated with thick mucosal folds, nodularity and aphthous erosions at endoscopy. It has been described in association with *H. pylori* infection and, also, celiac disease (celiac sprue). Histology shows an infiltrate of the lamina propria in the antrum or body by plasma cells, lymphocytes and rare neutrophils, and a marked intraepithelial infiltrate with T lymphocytes.

Eosinophilic gastritis is associated with peripheral eosinophilia and eosinophilic infiltration of the stomach, involving one or more layers of the gastrointestinal tract (mucosa, muscle or subserosa). Endoscopy may show pylori obstruction, prominent gastric folds, nodularity or ulceration, and histology is characterized by eosinophilic infiltration (> 20 per high power field), eosinophilic pit abscesses, necrosis and epithelial regeneration. Severe disease and symptoms may require corticosteroid therapy.

1.3.3. Hypertrophic Gastropathies

There are numerous causes of thickened gastric folds seen on endoscopy or diagnostic imaging (Table 2). Ménétrier's disease is associated with protein- losing gastropathy and hypochlorhydria whereas hyperplastic, hypersecretory gastropathy is associated with increased or normal acid secretion and hyper- plasia of the parietal and chief cells, with or without protein loss. Endoscopy, in both cases, typically shows irregular hypertrophic folds involving the body of the stomach, although there is a polypoid variant that resembles multiple hyperplastic gastric polyps. The characteristic histological features are foveolar hyperplasia with cystic dilation; inflammatory infiltrates may be present, as in hypertrophic lymphocytic gastritis, but this is variable. Ménétrier's disease may resolve spontaneously;symptomatic treatment includes acid antisecretory agents (H2-RAs, PPIs), anticholinergics and a variety of other, empirical therapies, including octreotide and corticosteroids. Gastric resection for refractory protein loss, hemorrhage or obstruction is a last resort. Zollinger-Ellison syndrome, due to ectopic secretion of gastrin, responds well, symptomatically, to high-dose PPI therapy and, if a gastrinoma can be identified, surgery may be curative.

Table 2. Causes of thick gastric folds seen on an upper GI series or EGD

- o Folds not actually thickened (barium study is wrong – ie. varices)
- o Malignant infiltration – adenocarcinoma, lymphoma, MALT lymphoma, linitis plastica
- o Benign infiltration -granulomas:e.g. sarcoidosis, TB, Crohn's severe gastritis (ethanol, *H. pylori*), Menetriers disease (hyperplasia) eosinophilic gastritis, lymphocytic gastritis, acute *H. pylori* gastritis
- o Multiple gastric polyps (HNPCC, FAP, fundic glands)
- o Hypersecretion (Zollinger-Ellison Syndrome)
- o Fundal varices
- o Worms

Abbreviations: EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; GI, gastrointestinal; TB, tuberculosis

First Principles of Gastroenterology and Hepatology   A. B. R. Thomson and E. A. Shaffer

Figure 5. Hypertensive gastropathy
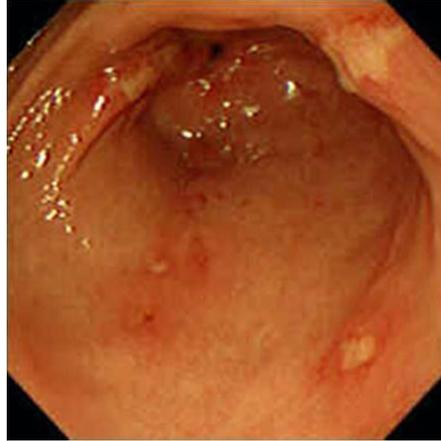
Figure 6. NSAID gastropathy

Figure 7. Portal hypertensive gastropathy

Figure 8. Watermelon stomach

Table 3. Potential causes of inadequate PPI response

- ➢ **Drugs**
  - o Non-adherence to PPI
  - o PPI not given 30 minutes before breakfast (or first meal of the day in shift worker)
  - o Other medication (nitrites, calcium channel blockers)
  - o Rapid metabolism of PPI
  - o Reduced bioavailability

- ➢ **Lifestyle**

- ➢ Large volume regurgitation and need for other drugs
  - o Posture (bending, lack of head of bed elevation)
  - o Increased BMI / increased waist girth
  - o Previous myotomy, hemigastrectomy
  - o Delayed gastric emptying

- ➢ Other causes of esophageal symptoms
  - o Esophagus
    - – Other causes of esophagitis
    - – non-acid GERD
    - – motility disorders; DES; achalasia
    - – functional, hypersensitive
    - – pill esophagitis, NERD, esophageal cancer, skin disease with esophagitis (Epidermolysis dissecans, Mucocutaneous candidiasis), eosinophilic esophagitis, infectious esophagitis (candida, HSV, CMV
  - o Stomach-- Hypersecretory state, nocturnal acid breakthrough, gastroparesis
  - o Small Intestine-- Bile reflux
  - o Colon – GERD associated with IBS
  - o Other diagnoses (ie. Heart disease)

Abbreviations: CMV, cytomegalovirus; DES, diffuse esophageal spasm; GERD, gastroesophageal reflux disease; HSV, herpes simplex virus; IBS, irritable bowel syndrome; NERD, normal esophagus reflux disease; PPI, proton pump inhibitor

1.3.4. Miscellaneous Gastritides

Gastritis cystica profunda is a rare sequela of partial gastrectomy with gastro-jejunostomy but it may also develop in the absence of prior gastric surgery. Endoscopy typically shows multiple exophytic gastric masses, which on sec- tion reveal multiple cysts. At histology, foveolar hyperplasia is accompanied by cystic glands that extend through the muscularis mucosae into the submucosa and muscularis propria. It may be associated with chronic atrophic gastritis, hyperplasia or primary gastric stump cancer after surgery.
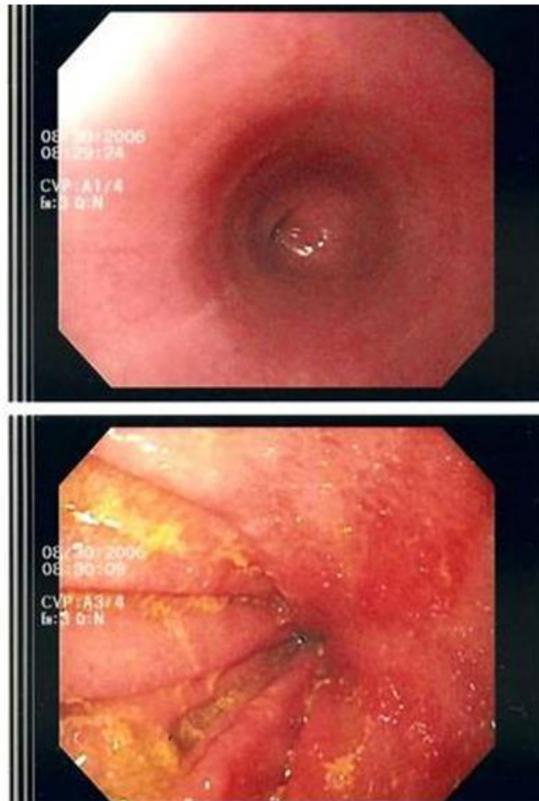
Figure 9. Bile gastritis

2. Gastric Polyps and Gastric Malignancy

There are numerous types of gastric polyps (Table 4) which are usually incidental findings with little risk of developing into cancer. *Gastric polyps* are gastric epithelial or non-epithelial protrusions observed either endoscopically or radiologically. The non-epithelial polyps arise from the mesenchymal tissue of the submucosa (such as a leiomyoma). The epithelial polyps are most common, and are often multiple, hyperplastic polyps. Infre- quently, adenomatous or villoadenomatous polyps, which are often singular, occur. Duodenal adenomatous polyps may also be found in patients with Familial Adenomatous Polyposis (FAP) Syndrome.

Individuals with a parent or sibling with gastric cancer are three times as likely to develop gastric cancer as the general population. People born in a country where gastric cancer is common (e.g., Japan or Eastern Europe) are also at increased risk, even if they have lived in North America for many years. Although regular screening is not warranted in either case, minor symptoms should be promptly and thoroughly investigated.

In the USA over 20,000 new cases of gastric adenocarcinoma are diagnosed annually, with the majority detected at an advanced stage with 1- and 5-year survival rates of 30% and 10%, respectively. In Canada there were 2,800 new gastric cancer cases in 2001 (8 per 100,000) and 1,950 deaths.

There are numerous risk factors associated with the development of gastric adenocarcinoma (Table 5). The incidence of gastric adenocarcinoma has been falling dramatically in North America from ~ 30 per 100,000 in the 1930s to 6–8 per 100,000 at present. There is a disparity in adenocarcinoma incidence between first- and second-generation immigrants, suggesting both genetic and lifestyle or environmental factors together contribute to the risk for cancer. Genetic factors that increase the risk include low gastric acid secretory status and the presence of pro-inflammatory genes such as interleukin-1ß, which is associated with gastric acid hyposecretion. Several lifestyle factors including diet and smoking increase the risk of gastric cancer but these are potentially modifi- able. Infection with *H. pylori* is strongly associated with gastric malignancy and cancer develops in about 1% of those infected.

Table 4.The endoscopic characteristics and diagnostic criteria for types of benign gastric polyps

Polyp type	Location	Size	Endoscopic appearance	Pathological features	Comments
Fundic gland (75%)	Fundus and upper body	<1 cm	Smooth, glassy, transparent; usually multiple polyps are found	o *Helicobacter pylori*-associated gastritis is rare	o Associated with PPI use, may regress o Dysplasia found in patients with FAP o Fundic gland polyp: distorted glands and microcysts lined by parietal and chief cells; no or minimal inflammation
Hyper-plastic (20%)	Random, adjacent to ulcers or stoma sites, or in the cardia if related to acid reflux	Generally <1 cm	Small polyps have a smooth dome; large polyps are lobulated, and erosions are common	o Atrophic gastritis with intestinal metaplasia o *Helicobacter pylori*-associated gastritis (25%), dysplasia is rare (<3%) and found in polyps <2 cm	o *Hyperplastic* elongated, cystic, and distorted foveolar epithelium, marked regeneration; stroma with inflammation, edema, and smooth muscle hyperplasia

Polypoid lesion	Gastric location	Size	Endoscopic appearance	Pathological features	Comments
Adenoma	*Incisura angularis*, found in the antrum than fundus	<2 cm	Velvety, lobular surface; exophytic, sessile or pedunculated; usually solitary (82%)	o Atrophic gastritis with intestinal metaplasia o May be accompanied by coexistent carcinoma	o*Adenoma* dysplastic intestinal- or gastric-type epithelium with variable architecture
Inflam-matory fibroid	Submucosal, found near the pyloric sphincter	Median 1.5 cm; generally <3 cm	Single, firm, sessiole, well-circum-scribed, ulceration is common	o Pernicious anemia commonly found; atrophic gastritis o Genetic mutations are common	oCD34+ spindled stromal cells, inflammatory cells, and thin-walled vessels in a mmyxoid stroma
Peutz-Jeghers	Random	<1 cm	Pedunculated with a velvety or papillary surface	o Normal o Risk of adeno-carcinoma rare in gastric polyps	
Juvenile	Found more in the body than in the antrum	Variable	More rounded than hyperplastic polyps; superficial erosions; multiple polyps are usually found	o Normal o Polyps may exclusively involve stomach risk of adeno-carcinoma but rare in gastric polyps	
Xanthoma	Antrum, lesser curvature, prepyloric	<3 mm	Can be multiple in groups; sessile, pale-yellow nodule or plaque	o Chronic gastritis o No association with hyper-lipidemia	oXanthom aggregates of lipid-laden macrophages in the lamina propria

Polypoid lesion	Gastric location	Size	Endoscopic appearance	Pathological features	Comments
Pancreatic heterotopia	Antrum, prepyloric	0.2-4.0 cm	Solitary; dome-shaped with central dimple; smooth surface	o Normal o Very rare instances of associated pancreatitis, islet-cell tumors, adeno-carcinoma	o *Pancreatic heteropia* normal components pf pancreatic parenchyma
Gastrointestinal stromal tumor	Random, submuco-sal	Variable (median 6 cm)	Well-circum-scribed; overlying mucosa may be ulcerated	o Normal o 25% are malignant; risk of aggressive behaviour depends on size and mitotic count	o CD117+, CD34+ spindle cell or epitheliod cell tumor with variable pattern, mitoses, and stroma
Carcinoid	Body and fundus	<2 cm, larger if sporadic	Hypergastri-nemic lesions: firm, yellow, broad-based and multiple. Sporadic lesions: large and single	o Autoimmune atrophic gastritis with intestinal metaplasia parietal cell hyperplasia in ZES normal mucosa if lesion is sporadic o Associated with hypergastri-nemia, autoimmune atrophic gastritis, ZES or MEN	o *Carcinoid* nodular proliferation of neuroendocrine cells >500 µm in diameter

Abbreviations: FAP, familial adenomatous polyposis; MEN, multiple endocrine neoplasia; ZES, Zollinger-Ellison syndrome

Adapted from: Carmack SW, et al. *The American Journal of Gastroenterology* 2009;104(6): 524-532.; and Carmack SW, et al. *Nat Rev Gastroenterol Hepatol* 2009;6(6): 331-34.

Table 5. Risk factors associated with the development of gastric adenocarcinoma

- o Genetic--First degree relative with gastric cancer (hereditary diffuse gastric cancer) (2-3 fold increased risk): with mutations in E-cadherin CDH1 gene
- o HNPCC >> APC
- o Polyps--adenomatous gastric polyps (HNPCC, APC), Peutz-Jeghers syndrome, hamartomas, Menetrier's syndrome
- o *Gastric atrophy--H.pylori* infection, pernicious anemia, chronic atrophic gastritis, subtotal surgical resection with vagotomy for benign gastric ulcer disease
- o Diet-- salted, pickled or smoked foods, low intake of fruits and vegetables
- o Life Style--Smoking (EtOH is not an independent risk factor)
- o Esophageal --Barrett's esophagus (cancer of cardia)

Abbreviation: HNPCC, hereditary nonpolyposis colon cancer

Adapted from: Houghton JM and Wang TC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006*:* pg 1149.

2.1. Environmental Risk Factors

  Dietary factors that contribute to gastric cancer include a high dietary salt and nitrate/nitrite intake, low fruit and vegetable intake, and the use of tobacco. The INTERSALT Cooperative Research Group (39 populations, 24 countries) confirmed an association between stomach cancer mortality and 24-hour urinary sodium excretion, and 24-hour urinary nitrate excretion, in both men and women.

  Persons with the highest intake of vegetables have a significantly reduced risk of gastric cancer compared to those who consume no vegetables. Similar but weaker protective effects have also been observed for consumption of green and cruciferous vegetables.

  Current smoking adversely influences the risk for gastric cancer, and this risk increases with the intensity and duration of cigarette smoking.

Figure 10. Carcinoma of the gastric cardia
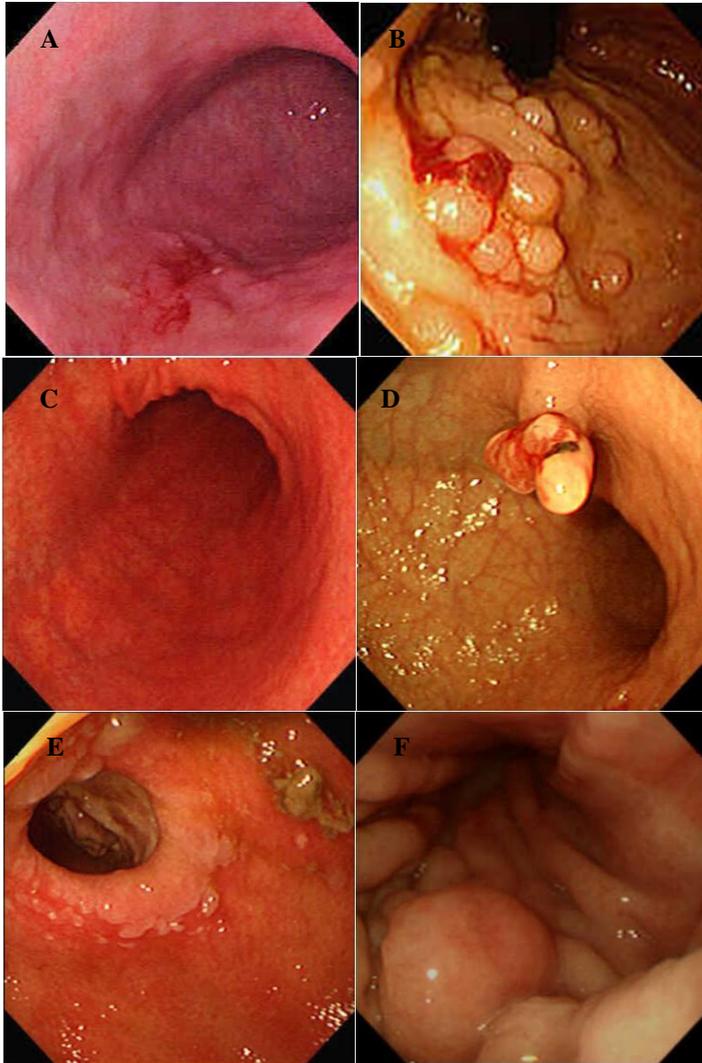
Figure 11. A) Early gastric cancer. B) Fundic gland polyps in FAP. C) Gastric atrophy D) Gastric polyps. E) Intestinal metaplasia in stomach. F) Gastric lymphoma.

In 1994, the International Agency for Research on Cancer (WHO) classified *H. pylori* as a group 1 carcinogen based on numerous studies that confirmed the association between *H. pylori* infection and gastric cancer rather than by direct cause and effect. Nested case-control studies showed an increase in the risk of cancer (odds ratios 2.5–6.0) while meta-analyses of cohort or case- controlled studies reported summary odds ratios for gastric cancer in those infected with *H. pylori* of 1.92–2.24. Younger individuals had a

higher risk for gastric cancer than older patients, presumably because of their having a longer duration of exposure. Infection with *H. pylori* is strongly associated with gastric malignancy and cancer develops in about 1% of those infected. Eradication of *H. pylori* reduces the risk of recurrence of early gastric cancer. Population studies have not proven that the eradication of *H. pylori* prevents the development of gastric cancer, but it may be that treatment of the infection must begin at a much earlier age before the progression of the inflammatory process has occurred (Table 6).

2.2. Gastritis, Intestinal Metaplasia and Gastric Cancer
2.2.1. Adenocarcinoma

Almost a decade before *H. pylori* was isolated, Correa proposed the concept of an inflammatory cascade initiated by an acute gastritis progressing to a chronic atrophic gastritis as the basis for gastric carcinogenesis. *H. pylori* infection is the most common cause of chronic gastritis. In a proportion of patients with chronic atrophic gastritis, intestinal metaplasia develops and, in a much smaller proportion, dysplasia and subsequently cancer (Table 5). Recent studies have shown the importance of inflammation, arising from the initial *H. pylori* infection with resultant gene polymorphisms, which increase the risk of gastric cancer. Patients with the interleukin-1 gene cluster polymorphism, which may enhance production of the proinflammatory cytokine interleukin-13, are at increased risk of *H. pylori*-induced hypochlorhydria and gastric cancer. Thus, host genetic factors that affect interleukin-1ß production and hypochlorhydria may influence gastric cancer risk in those infected with *H. pylori*. In relatives of index cases of gastric cancer who had *H. pylori* infection, atrophy and hypochlorhydria were significantly more common than in non-infected relatives.

Table 6. The annual risk of progression of gastritis to gastric cancer

Pathology	Risk of GCa per year	Recommended EGD/Biopsy follow-up
➢ Atrophic Gastritis	o 0.1%	- None
➢ Intestinal Metaplasia	o 0.3%	- 2-3 years
➢ Mild to moderate dysplasia	o 0.6%	- 1 year
➢ Severe dysplasia	o 6.0%	- Definitive therapy (EMR)

Abbreviation: EGD, esophagogastroduodenoscopy ; EMR, endoscopic mucosal resection
Adapted from: De Vries AC, et al. *Gastroenterology* 2008;134:945-52.

The presence of other pro-inflammatory polymorphisms, including inter- leukin-13, interleukin-1 receptor antagonist, tumour necrosis factor-**a** and interleukin-10, confer an increasingly greater cancer risk. Such exciting advances in the genetics of gastric cancer promise a means to identify early those who are at risk of this serious malignancy.

2.2.2. Neuroendocrine Tumors

Table 7. Secretory products and clinical characteristics of foregut, midgut and hindgut carcinoids (neuroendocrine tumors).

Location	Secretory products	Clinical characteristics	Carcinoid syndrome
o Foregut-Stomach, duodenum, pancreas	Serotonin, histamine	Indolent except type 3 gastric carcinoid	Rare
o Mid gut- Jejunum, ileum, appendix, ascending colon	Serotonin, prostaglandins, polypeptides	Often multiple, usually in ileum	Classic, but present in <10% of cases
o Hindgut- Transverse, descending, and sigmoid colon and rectum	None	Indolent except in colon	Rare

Printed with permission: Rancis, Dawn L. *Gastritis. Mayo clinic Gastroenterology and Hepatology Board Review*. Page 87.

2.3. Diagnosis and Staging of Gastric Cancer

Diagnosis of gastric cancer should be suspected in patients over the age of ~ 50 years with epigastric symptoms of new onset, including early satiety, anorexia, nausea and vomiting, and especially when there are associated alarm symptoms of anemia, weight loss etc. However, by this stage the disease is likely to be advanced. Confirmatory diagnosis is usually made at endoscopy when biopsies and the intraluminal extent can be determined. Routine barium meal is of little value in diagnosis although the tumour will often be seen. Ultrasound may sometimes be helpful and abdominal CT scan can be used to determine the extent of disease and any metastatic spread. Gastric cancer may spread within the abdomen, for example to the ovaries (Krukenburg tumour).
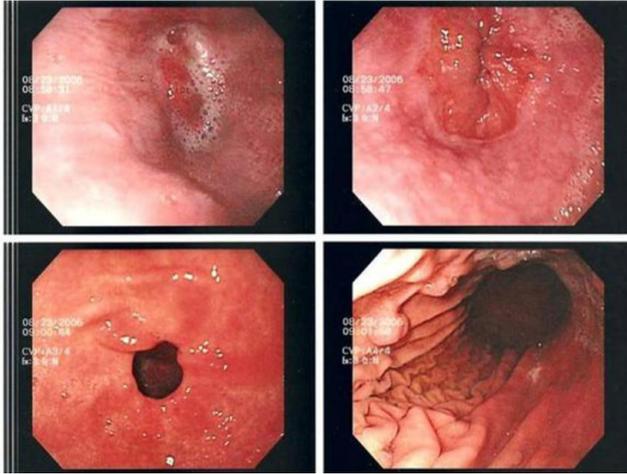
Figure 17. Fundic gastric polyps
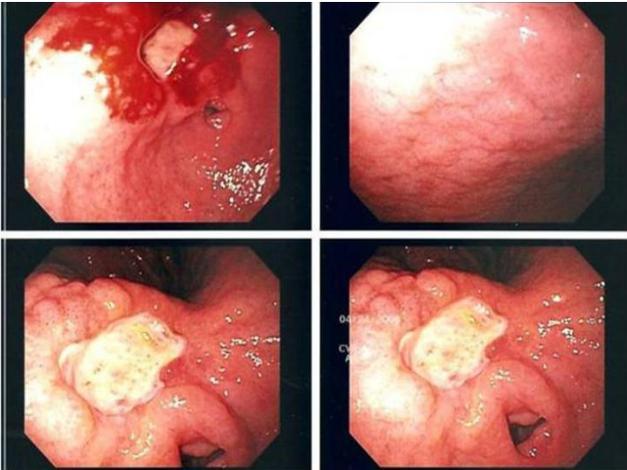
Figure 18. GU, possible gastric Ca

While the guidelines for dyspepsia take into account the need to attempt to prevent a missed diagnosis of gastric cancer, in fact persons with fastric polyps are usually asymptomatic, and those with gastric cancer usually present with alarm sysmptoms such as weight loss of bleeding, rather than with dyspepsia. Nonetheless, it is important to appreciate that there are many causes of thickened gastric folds and types of gastric polyps. The finding of thickened gastric folds or polyps on an upper GI series mandates the performance of an EGD to obtain multiple biopsies, which will allow for a diagnosis to be made and an appropriate management plan established. For the purpose of providing the patient with a prognosis, it is important for the endoscopist to provide the macroscopic type of the gastric cancer (Table 8).

While gastric cancer is usually diagnosed late and there is no universally-accepted reference standard chemotherapy, meta-analyses of randomized trials have shown a benefit for first-line combination therapy (Power et al. 2010). Clinocopathologic factors have been identified with improved several, and targeted therapy with for example anti-angiogenic and anti-Her$_2$ therapy, may in a subset of patients provide survival for more than two years.

Staging of the tumour is usually undertaken to determine prognosis and progress of the cancer. The widely used TNM (Tumour, Node, Metastasis) system is usually used and can help decide on the best course of treatment. Staging determines characteristics of the tumour and the extent of spread to other parts of the body.

Table 8. Macroscopic types of gastric cancer

Type	Japanese classification	Paris classification
0	Superficial, flat tumors with or without minimal elevation or depression	Superficial polypoid, flat/depressed, or excavated tumors
0I	Protruded	Polypoid
0IIa	Superficial and elevated	Non-polypoid and nonexcavated, slightly elevated
0IIb	Flat	Non-polypoid and nonexcavated, completely flat
0IIc	Superficial and depressed	Non-polypoid and nonexcavated, slightly depressed without ulcer
0III	Excavated	Nonpolypoid with a frank ulcer
1	Polypoid tumors that are sharply demarcated from the surrounding mucosa and are usually attached on a wide base	Polypoid carcinomas that are usually attached on a wide base
2	Ulcerated carcinomas that have sharply demarcated and raised margins	Ulcerated carcinomas that have sharply demarcated and raised margins
3	Ulcerated carcinomas that have no definite limits and infiltrate into the surrounding wall	Ulcerated, infiltrating carcinomas that have no definite limits
4	Diffusely infiltrating carcinomas in which ulceration is not usually a marked feature	Nonulcerated, diffusely infiltrating carcinomas
5	Carcinomas that cannot be classified into any of the above types	Unclassifiable advanced carcinomas
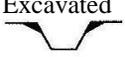
According to Japanese classification of gastric carcinoma, for the combined superficial types, the type occupying the largest area should be described first, followed by the next type (e.g. IIc+III). Types 0 I and 0 IIa are distinguished from each other by lesion thickness: type 0 I lesions have thickness more than twice that of the normal mucosa and type 0 IIa lesions have a thickness up to twice that of the normal mucosa and type 0 IIa lesions have a thickness up to twice that of the normal mucosa. Modified from data presented in the Japanese classification of gastric carcinoma and the Paris endoscopic classification of superficial neoplastic lesions.

Printed with permission: Yamamoto H. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(9): page 513.

2.4. Treatment of Gastric Cancer

Treatment of gastric cancer is usually surgical, although a palliative endo- scopic procedure with tumour debulking may be considered in patients unfit for a definitive procedure. Surgical approaches involve partial, or sometimes total, gastrectomy depending on the location and extent of the tumour. The procedure may also involve removal of any lymph nodes involved in the malignancy. The more radical procedures will involve complex anastomosis to maintain continuity of the gut and esophago-jejunal anastomosis in the case of total gastrectomy. Careful long-term follow up of such patients is essential to maintain optimal nutritional status.

Radiation therapy and chemotherapy may also be used depending on the extent and stage of the tumour. Current chemotherapeutic agents may include epirubicin, cisplatin, 5-fluorouracil while the newer generation of chemother- apeutic agents, such as gemcitabine, irinotecan and paclitaxel and the recent introduction of "biological" or immunological treatments or vaccines, which block growth signals, inhibit angiogenesis, stimulate the bodies own immune system etc., offer new hope for patients with a condition that has traditionally carried a very poor outlook.

Because of the dismal prognosis of gastric cancer unless it is diagnosed early (such as may occur in Japan with gastric cancer screening programs), it is important to recognize the risk factors which are associated with the development of gastric adenocarcinoma (Table 10). There are no Canadian guidelines for screening for gastric cancer, and in our community those at highest risk of developing gastric cancer are those with a family history, and those with a personal history of an *H. pylori* infection for many years, such as First Nations persons, or new Canadians from high endemic risk areas. If a type of gastritis with a high risk of progression to gastric cancer happens to be identified (Table 6), the patient may be entered into a surveillance (follow-up) program.

2.5. Gastric Cancer Prevention

A healthy diet, rich in fruits and vegetables and low in salt, pickles, nitrates and nitrites is likely to carry a reduced risk of gastric cancer. It is not clear to what extent heredity is important although numerous reports of familial gastric cancer are documented. The common originating factor may still be infection with *H. pylori* in a household. New information on genetics will help clarify this. An important question that is not yet answered is whether widespread eradication of (or vaccination against) *H. pylori* infection will reduce or prevent gastric cancer. A large number of tri- als with differing endpoints is under way but it seems clear that treatment would need to be given relatively early in life before

intestinal metaplasia and dysplasia have occurred for cancer to be prevented. Guidelines in Canada recommend that *H. pylori* infection be eradicated whenever detected.

Table 9.Risk Factors Including Protective Factors for Gastric Adenocarcinoma

➢ Definite
- o *Helicobacter pylori* infection
- o Chronic atrophic gastritis
- o Intestinal metaplasia
- o Dysplasia
- o Adenomatous gastric polyps
- o Cigarette smoking
- o History of gastric surgery (esp. Billroth II)
- o Genetic factors
- o Family history of gastric cancer (first-degree relative)
- o Familial adenomatous polyposis (fundic gland polyps)
- o Hereditary nonpolyposis colorectal cancer
- o Peutz-Jeghers syndrome
- o Juvenile polyposis

➢ Probable
- o High intake of salt
- o Obesity (adenocarcinoma of cardia only)
- o Snuff tobacco use
- o History of gastric cancer
- o Pernicious anemia
- o Regular aspirin or NSAID use (protective)

➢ Possible
- o Low socioeconomic status
- o Menetrier's disease
- o High intake of fresh fruits and vegetables (protective)
- o High ascorbate intake (protective)

➢ Questionable
- o Hyperplastic and fundic gland polyps
- o High intake of nitrates
- o High intake of green tea (protective)

NSAID, nonsteroidal anti-inflammatory drug

2.6. Other Gastric Malignancies
- o *Gastric lymphoma* is a rare tumour representing between 2 and 7% of gastric malignancies. Lymphoma may be primary or secondary from a more general- ized lymphoma arising in other organs. Secondary lymphoma must be managed as part of the systemic disease.
- o *Mucosa-associated lymphoid tissue lymphoma* (MALT) is increasingly recognized and may also be associated with *H. pylori* infection. Treatment may lead to remission of the disease but the patient remains at risk of a recurrence in the event of reinfection.

o *Familial adenomatous polyposis*, may involve the stomach and in patients in whom this is detected in the rectum and colon, a full gastrointestinal survey with endoscopy and radiology is necessary with appropriate ongoing surveillance where indicated.
o *Neuroendocrine tumors*
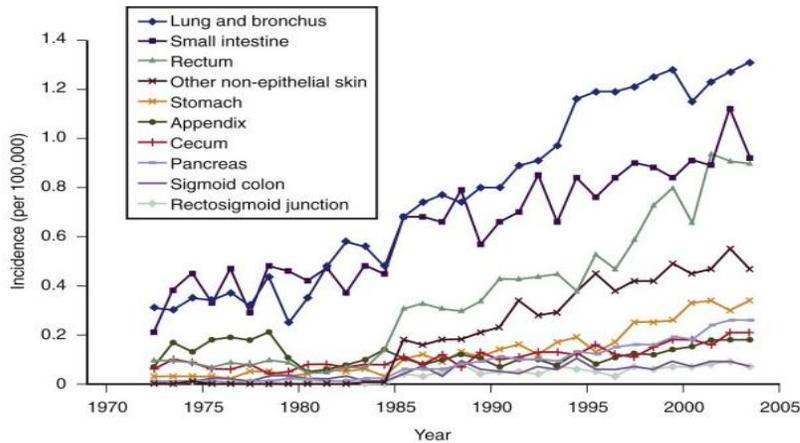
Figure 19. Incidence of different subtypes of neuroendocrine tumors, 1970 to 2005, from the Surveillance Epidemiology and End Results (SEER) data base., Note the significant increase in most subtypes of neuroendocrine tumors since the 1970s.(From Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet* Oncol 2008; 9:61-72.).

3. Miscellaneous Gastric Diseases

o *Gastric volvulus* is a rare cause of acute upper abdominal pain and vomiting and can be partial (antral) or total (entire stomach). These obstructions can arise by themselves, or as torsion within a hiatus hernia. Volvulus within a hernia is not uncommon in the elderly and may be asymptomatic. The belief that twisting obstruction poses an important risk to the blood supply is probably unjustified. Gastric aspiration is followed by surgical relief of the volvulus in those who present with obstruction.
o *Acute dilation* of the stomach can arise after any form of upper abdominal surgery, including cholecystectomy, and especially after vagotomy, after childbirth and in diabetic coma. The causes are uncertain. Vomiting of relatively clear gastric contents is succeeded by the production of dirty brown or feculent material and the development of abdom- inal distention. Prompt decompression with a large-bore stomach tube and intravenous fluid replacement are required. After a variable interval the condition should then resolve spontaneously (Figure 20).

Figure 20. Acute Gastric Dilation

o   *Gastric rupture* is a rare, acute, nontraumatic, spontaneous rupture of the stomach, which is catastrophic and poorly understood. The majority of ruptures occur on the lesser curvature. They have also been reported to occur during upper gastrointestinal radiography using barium, sodium bicarbonate ingestion, nasal oxygen therapy, cardiopulmonary resuscitation and labour, and during the postpartum period.

o   *Hypertrophic pyloric stenosis* is an idiopathic condition that may occur in infants or adults. The muscle of the pyloric canal is unduly hypertrophied. Infantile hypertrophic pyloric stenosis is more common in boys than in girls (the sex ratio is approximately 10:1), is a frequent anomaly (its incidence is about 3 per 1,000 live births) and is thought to be due to a combination of genetic predisposition and some abnormality of fetal or early postnatal development. Symptoms usually develop in the first few weeks after birth and characteristi- cally consist of copious projectile vomiting of the gastric contents after feeding. On examination there is usually visible gastric peristalsis; a lump can be felt abdominally in the region of the pylorus. Barium-meal examination is not usu- ally necessary but will confirm the presence of a narrow segment, 1–2 cm long, at the pylorus. The condition must be distinguished clinically from esophageal atresia (which involves difficulties with swallowing, with onset at birth) and duodenal obstruction/atresia (which involves bile-stained vomitus). A minor proportion of all cases settle in the first two to three months with conservative management with anticholinergic drugs, but most patients will require early surgery with Ramstedt's procedure (pyloromyotomy).

o   *Gastric diverticula* occur most commonly near the cardia on the lesser curve, but occasionally are found in the prepyloric region. They seldom cause symptoms. Their principal importance lies in the likelihood of confusion with gastric ulceration on barium radiography.

o *Pseudolymphoma* is localized lymphoid hyperplasia of the stomach. The lesions are raised, flat or nodular folds, and are often associated with gastric ulceration. The etiology of this condition remains unclear, but *H. pylori* infec- tion has been implicated. It is difficult to exclude lymphoma using radiology or endoscopic biopsy, thus, a resected specimen is required for diagnosis.

o *Gastric bezoars* are persistent concretions found in the stomach and con- sist of a variety of substances, most commonly plant and vegetable fibres (phytobezoars), persimmons (disopyrobezoars) or hair (trichobezoars). They most commonly occur in patients with previous gastric surgery or delayed gastric emptying and often produce symptoms including early satiety, abdominal fullness and epigastric pain. They may also occur in patients with behavioural disorders and the mentally challenged, especially when institu- tionalized. They can be complicated by gastric ulcer, secondary anemia and bleeding. Treatment methods include endoscopic removal or destruction, oral enzymatic therapy to dissolve the bezoar and metoclopramide.

Abbreviations

CE	Capsule endoscopy
COPD	Chronic obstructive pulmonary disease
COXIBs	COX-2 inhibitors
CV	Cardiovascular risk
CVA	Cerebrovascular accident
DBE	Double balloon enteroscopy
EGD	Esophagogastroduodenoscopy
EGG	Electogastogram
ET	Endoscopic hemostatic therapy
ET	Eradication therapy
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
GAVE	Gastric antral vascular ectasia
GVHD	Graft-versus-host-disease
H2RA	H2 receptor antagonist
HCl	Hydrochloric acid
Hp	*Helicobacter pylori*
ITP	Idiopathic thrombocytopenic purpura
MRI	Magnetic resonance imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVUGIB	Non-variceal upper GI bleeding
OR	Odds ratio
PE	Push enteroscopy
PHG	Portal hypertensive gastropathy
PPIs	Proton pump inhibitors
PUD	Peptic ulcer disease
SHR	Endoscopic stigamata of recent hemorrhage.
SIDS	Sudden infant death syndrome
SPECT	Single photo emission computed tomography

TSH   Thyroid ultrasound
UGIB   Upper GI bleeding
US   Ultrasonography
ZES   Zollinger Ellison syndrome

168
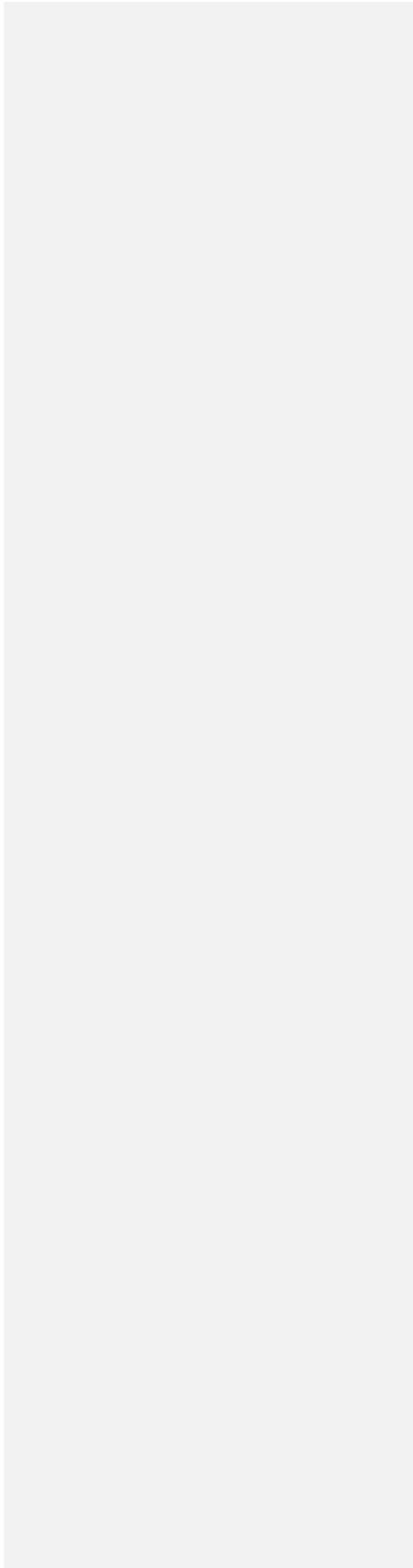
Chapter 6: The Small Intestine Intestinal
Digestion and Absorption in Health
A.B.R. Thomson and H.J. Freeman

1. Anatomy

The small intestine is a specialized abdominal tubular structure with an adult length of about 6 m, depending on the method of measurement. The proximal portion, the *duodenum,* consists of the: bulbar, descending, transverse and ascending portions. Most of the duodenum is retroperitoneal, wrapped around the head of the pancreas. As a result, inflammatory or neoplastic masses in the pancreas sometimes compress the duodenum. From the ligament of Treitz, the jejunum are suspended on a mesentery crossing from left upper to right lower quadrants. Then, the small intestine enters the large intestine at the ileocecal "valve." The latter is not a true valvular structure but a physiological sphincter that acts to reduce cecal reflux into the small intestine.

The plicae circulares are more evident in proximal jejunum compared to distal ileum. The narrower ileal lumen is more prone to obstruction. Lymphoid follicles (aka Peyer's patches) are visualized along the length of small intestine, particularly in distal ileum. Although the proximal duodenum derives some arterial supply from the celiac axis and its branches, and the rest of the small intestine derives mainly from the superior mesenteric artery. Veins follow the arterial supply, with the superior mesenteric vein flowing into the portal vein. Lymphatic drainage also follows these vascular structures flowing into lymph nodes and eventually the cisterna chyli, thoracic duct and left subclavian vein. Extrinsic innervation derives from the vagal nerve parasympathetic, while upper thoracic sympathetic fibers also supply the small intestine. Gut neurons project from the intestine to innervate the prevertebral sympathetic ganglia.

The intestinal wall is comprised of the mucosa, muscularis propria, submucosa and serosa. The serosa is a layer of mesothelial cells extending from the peritoneum. The muscularis propria includes both the outer longitudinal and inner circular layers separated by ganglion cells of the myenteric plexus (Auerbach's plexus). The submucosa consists of a connective tissue framework, plus lymphocytes, plasma cells, mast cells, eosinophils, macrophages and fibroblasts. There are also numerous ganglion cells and nerve fibers (Meissner's plexus) as well as vascular and lymphatic structures in the submucosa. The mucosa is separated from submucosa by a layer of muscle cells, the muscularis mucosae. The epithelial layer of the mucosa is divided into villus and crypt regions. Villi are fingerlike projections extending into the small intestinal lumen. They are longer in the jejunum compared to the ileum. Villi are covered with enterocytes which are specialized for digestion and absorption, along with goblet cells and intraepithelial lymphocytes. Cells from several adjacent crypts migrate into each villus and differentiate during their migration and eventual extrusion from the villus with a turnover of four to six days.

Stem cells, located in the base of crypts, are pluripotential cells that do not migrate from the crypt bases. Undifferentiated crypt cells are the most common crypt cells that may proliferate rapidly, but they have poorly developed structure, including intracellular organelles and microvilli. Paneth cells are characterized by eosinophilic granules that remain in the crypt bases and contain growth factors, digestive enzymes and antimicrobial peptides. Goblet cells are epithelial cells that contain visible mucins that may be discharged into the intestinal lumen, and play a role in immune defense. Enteroendocrine cells contain secretory granules that may influence epithelial function through enterocyte basolateral membrane receptors. Enterocytes are polarized epithelial cells containing apical and basolateral membrane domains. The apical, microvillus brush border membrane faces the lumen, contains a complement of digestive enzymes, transporters and ion channels, different from

those on the basolateral membrane. The enterocytes are connected by junctional complexes, forming a permeability barrier to the contents of the intestinal lumen. This polarized distribution of membrane proteins permits vectorial transport that differs in various regions of the small intestine. The basolateral membrane also has nutrient and electrocyte transporters as well as receptors for growth factors, hormones and neurotransmitters. Intestinal immune system includes M-cells and intraepithelial lymphocytes (IELs). M-cells are epithelial cells overlying lymphoid follicles that bind, process and deliver pathogens directly to lymphocytes, macrophages or other components of the immune system. IELs are specialized memory T-cells that migrate from the peripheral circulation to intercalate between the basolateral membranes of epithelial cells.

There is a complex vascular and lymphatic network extending through the villus core that is involved in signal and nutrient trafficking to and from the epithelial cell layer. The enteric nervous system (ENS) is even more complex, forming a myenteric and submucosal plexus, as well as containing intrinsic sensory neurons, interneurons for reflex activities and motor neurons that mediate actions of the enteric smooth muscle, glands and blood vessels. The interstitial cells of Cajal (ICC), have pacemaker activity with development of slow waves that electrically couple to smooth muscle cells. This leads to propulsive activity that promotes luminal movement of material from the proximal into the distal intestine.

2. Motility

The main function of the small intestine is digestion and absorption of nutrients. The role of small bowel motility is to mix food products with digestive enzymes (chyme), to promote contact of chyme with the absorptive cells over a sufficient length of bowel and to propel undigested material into the colon. Food in the stomach is churned into smaller and smaller particles. Once those particles are < 2 mm in size, they are pushed into the duodenum by co-ordination of contraction of the antrum and the relaxation of the pylorus. The rate of emptying of the stomach may be slowed by inhibition occurring from the duodenum or from the ileum. Receptors in the mucosa sense calories, osmolality, acid, fatty acid concentrations and slow emptying when these are high. Fatty acid in the ileum release glucagon-like peptide (GLP-1 or -2), peptide tyrosine-tyrosine (peptide YY); these peptides also slow gastric emptying by a process called the "ileal break". Well-organized motility patterns occur in small intestine to accomplish these goals in the fed as well as the fasting. During fasting, there is a migrating motor complex (MMC) which starts in the lower esophagus. Sweeping through the stomach, it removes debris and residual material not emptied with the last meal. This MMC is characterized by a front of intense spiking activity (phase III activity) that continues to migrate down the entire small intestine. As the activity front reaches the terminal ileum, another front develops in the gastroduodenal area and progresses down the intestine. The purpose of phase III myoelectric and contractile activity is to sweep remnants of the previous meal into the colon, and prevent stagnation and bacterial overgrowth.

During meals, this MMC cycle is interrupted, and the motility pattern in the small bowel becomes an irregular spiking activity called the "fed pattern." This fed pattern of motility mixes but does not seem to move intestinal contents forward to any great extent but does mix these contents with digestive juices, spreading them again and again over the absorptive surface of the brush border. Diarrhea can occur when this normal fed pattern is replaced by aggressive propulsive rather than mixing contractions.

An overview of the motor function of the gastrointestinal tract (GIT) will be given, and in later sections motility will be considered in specific organ-related sections such as esophagus, stomach, small intestine and colon. The enteric nervous system (ENS) is comprised of efferent intrinsic and extrinsic motor neurons, interneurons, and afferent sensory neurons. The extrinsic afferent innervation of the intestine is supplied by the vagus nerve; over 80% of the vagal fibers are afferent, 20% are efferent (motor). The sensory aspect will be discussion with a consideration of the pain arising from IBS, the so-called irritable bowel (colon) syndrome.

The ENS has two major plexuses, the myenteric and the submucosal plexus (Figure 4). The ENS receives input from the central nervous system (CNS) and the autonomic nervous system (ANS). Enteric nerve cell bodies receive input from the sympathetic and parasympathetic components of the ANS. The myenteric plexus (Auerbach's plexus) runs between the inner circular and outer longitudinal smooth muscle and most of the nerves of this plexus project to these muscle layers. The submucosal plexus (Meissner's plexus and Schabadasch's plexus) runs between the inner circular muscle and the mucosa, and its nerves project to the mucosal nerves, as well as to the myenteric plexus.

The reflexes arising in the ENS begin from chemical or mechanical stimulation. Intrinsic primary afferent neurons (IPANs) are activated, and in turn the IPANs activate the enteric primary afferent neurons ("sensory", although not normally consciously perceived) in the submucosal and myenteric plexuses, which are integrated through interneurons, and produce a motor or secretory reflex response. Serotonin-containing enterochromaffin cells may be involved in the mucosal sensing of stimuli. There are numerous neurotransmitters in the GIT (Table 1).

Acetylcholine, tachykinins (e.g. substance P and neurokinins), and other peptides are released from the excitatory motor neurons, whereas the inhibitory motor neurons release nitric oxide (NO), adenosine triphosphate (ATP), VIP (vasoactive intestinal polypeptide, and PACAP (pituitary adenyl cylase-activating peptide). Nitric oxide (NO) synthase synthesized NO from arginine. NO diffuses rapidly from the activated neuron and binds to guanylyl cyclase on the myocyte membrane. Guanylyl cyclase converts GTP in the myocyte cytoplasm to cGMP, which relaxes the smooth muscle.

Table 1. Neurotransmitters in GI tract

➢ Myenteric plexus	o GABA (γ-aminobutyric acid)
	o Serotonin
➢ Submucosal plexus	o VIP, CGRP, SP, ACh
➢ Endocrine cells	o Somatostatin
➢ ANS Ganglia	o Serotonic
	o NYP (Neuropeptide Y), Somatostatin
➢ Excitatory, motor	o ACh, SP, NKA
➢ Inhibitory, motor	o NO, ATP, VIP, PACAP, β-NAD

Abbreviation: ANS, Autonomic Nervous System; ACh, Acetylcholine; NPY, Neuropeptide Y; SP, substance P; CGRP, calcitonic gene-related peptide; NKA, Neurokinin A; NO, Nitric

Oxide; PACAP, Pituitary adenyl cyclase-activating peptide; VIP, Vasoactive Intestinal Polypeptide.

The intrinsic motor neurons are both excitatory and inhibitory. They respond to slow as well as fast neurotransmitters. The fast excitatory neurotransmitter is acetylcholine, the slow excitatory transmitter, substance P. The fast inhibitory neurotransmitters are nitric oxide (NO), ATP and β-NAD (nucleotide β-nicotinamide adenine dinucleotide, and the slow inhibitory neurotransmitter is VIP. Polarized reflexes also result from the presence of a bolus in the intestinal lumen. The "law of the intestine" is the result of the ascending excitatory reflex and the descending inhibitory reflex of the excitatory and inhibitory motor neurons.

The myocytes form a syncytium, with each myocyte connecting with another through cell-to-cell contacts, called gap junctions. There is both electrical as well as mechanical connection, so the myocytes in each layer work as a contractile unit. In the GI tract, the muscle contractions may be tonic or phasic. These are confusing terms, because when we speak of the small intestine, for example as having tone, this is really a long-lasting tonic contraction. A phasic contraction is short in duration (about 1 to 5 seconds), and this is what we mean when we say the intestine is undergoing a contraction.

Intestinal tract smooth muscle has a basic electrical rhythm (BER), a slow wave of electrical potential, also known as pacemaker potential. The interstitial cells of Cajal (ICC, in the longitudinal or circular muscle) generates the BER, and this pacemaker potential is higher proximally than distally, e.g. 12 slow waves per minute in the duodenum,7 in the ileum. The ICC (interstitial cells of Cajal) are specialized mesenchymal cells that are placed closely to the myocytes and to the axons of neurons.

3. Nutrient Absorption
3.1. Iron

Iron is available for duodenal absorption from vegetables (non-heme iron, Fe^{3+}) and from meat (heme iron [Fe^{2+}], ingested as myoglobin and hemoglobin). Heme iron (ferrous, Fe^{2+}) is ingested as myoglobin and hemoglobin. In the presence of gastric acid, the globin molecule is split off myoglobin and hemoglobin, and its Fe^{2+} absorbed. Both heme and nonheme iron are absorbed most rapidly in the duodenum. Heme iron is better absorbed (10–20%), and is unaffected by intraluminal factors or dietary composition. Only 1-6% non-heme iron is absorbed, and absorption is influenced by luminal events such as gastric pH and binding substances in food (polytate, phosphate, phophoproteins). The average dietary intake of iron is 10–30 mg/day. Men absorb 1–2 mg/day, while menstruating women and iron-deficient persons absorb 3–4 mg/day. Non-heme iron (in the ferric, [Fe^{3+}] state), when ingested into a stomach unable to produce acid, forms insoluble iron complexes, which are not available for absorption (Figure 2).

INCREASE

Luminal

(1) Reducing agents
     HCL
     Ascorbic acid

(2) Chelating agents
     Organic acids
     Amino acids

 Mucosal

(3) Iron deficieny

DECREASE

Luminal

(4) Intraluminal binders
     Phosphate
     Phylates
     Oxalates
     Dietary fiber

Mucosal

(5) Proximal small
     bowel   disease
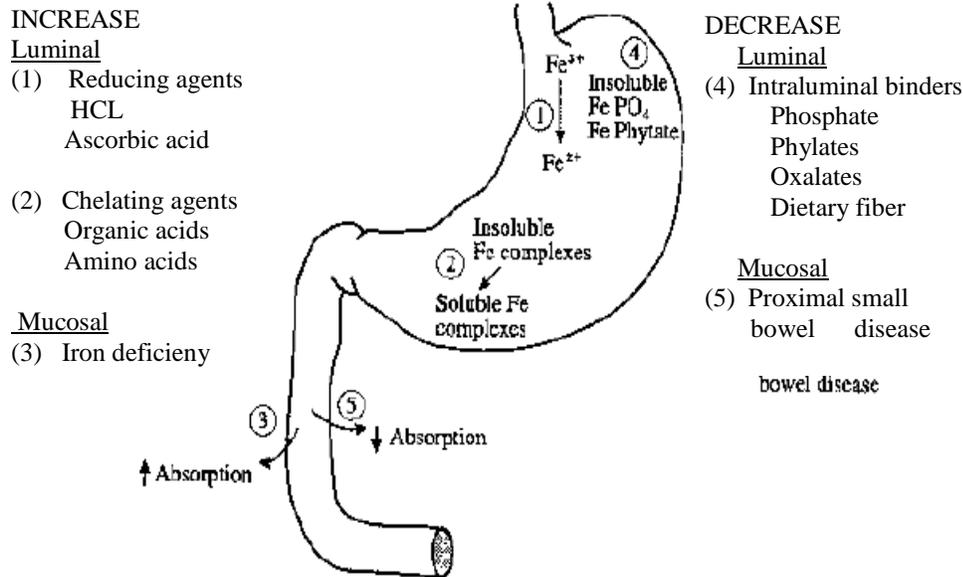
Figure 1. Factors that effect iron absorption. Nonheme ion absorption is affected both by intraluminal factors (1, 2 and 4) and by the total iron body content (3) as well as by small bowel disease (5). Heme iron absorption is altered only by those factors that affect the mucosa itself (3 and 5).

Source: Alpers DH. Absorption of water-soluble vitamins, folate, minerals, and vitamin D. In: Sleisenger MH, Fordtran JS (eds.), Gastrointestinal disease: pathophysiology, diagnosis, management. 3d ed. Philadelphia: WB Saunders, 1983:835.

In the presence of gastric acid and reducing agents (such as ascorbic acid, some sugars and amino acids). Ferric reductases in the BBM also reduces Fe^{3+} to Fe^{2+}. The Fe^{2+} is actively transported across the BBM by DMT_1 (divalent metal transporter 1), which is mostly in enterocytes at the top of the villus. DMT_1 is a proton symporter that also transports cobalt and manganese (Figure 3).
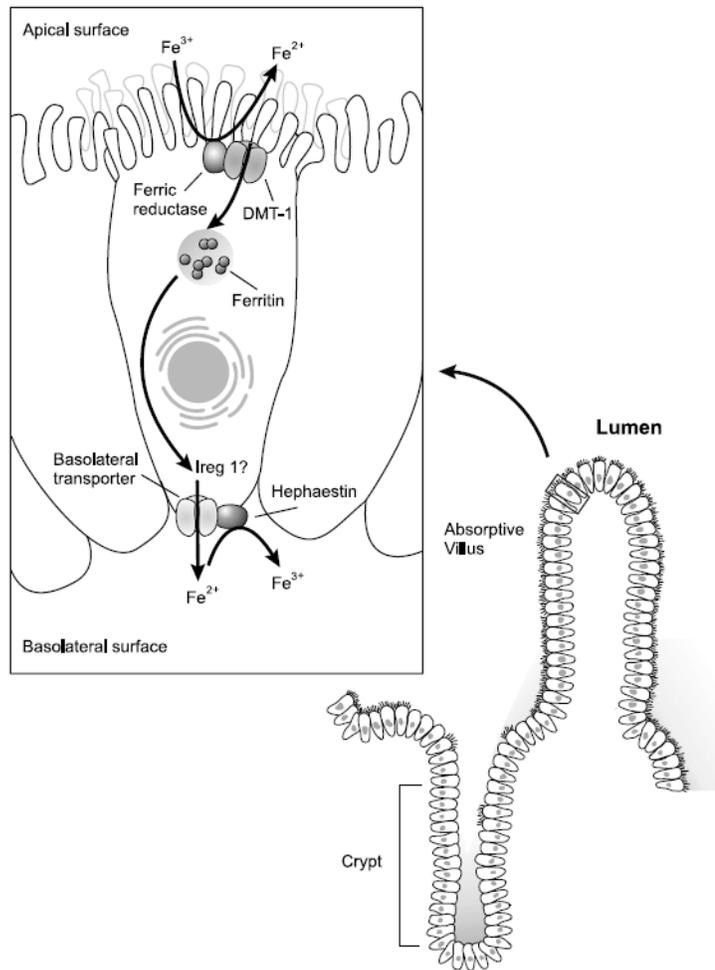
Figure 2. Intestinal absorption of iron. Iron is being transported across the brush-border membrane (BBM) by DMT (duodenal metal-transporter), and across the basolateral membrane possibly by Ireg 1, in conjunction with hephaestin, a ceruloplasmin-like molecule. Ferrureductase already in the BBM reduces Fe^{3+} to Fe^{2+} for transport by DMT. Absorption of iron is regulated by the amount of iron in the diet, body iron stores and by the activity of the bone marrow erythropoiesis.
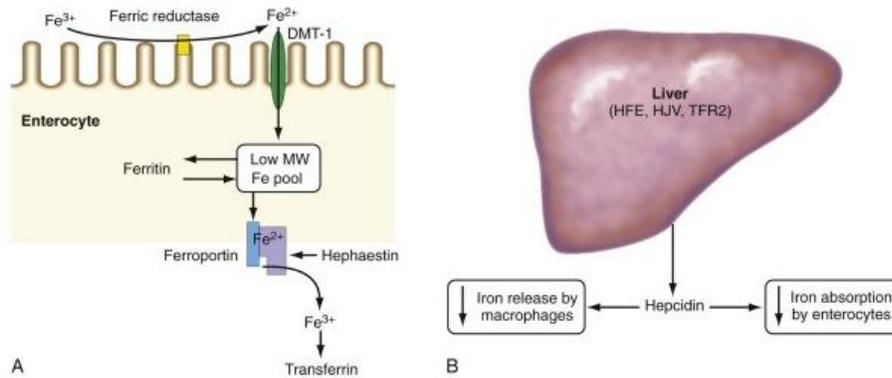
Figure 3. Iron absorption pathway in duodenal enterocytes and the role of hepcidin.
- o *A,* Duodenal enterocytes are the major site of iron absorption.
- o Before uptake, dietary ionic iron requires reduction from the ferric (Fe^{3+}) to the ferrous (Fe^{2+}) state.
- o This is accomplished by ferric reductases that are expressed on the luminal surfaces of enterocytes.
- o Ferrous iron is taken up by the apical transporter, DMT-1. Iron may be stored within the cell as ferritin, and then lost with the sloughed senescent enterocyte, or transferred across the basolateral membrane to the plasma.
- o This process occurs via the transporter ferroportin and requires oxidation of iron back to the ferric state by the ferroxidase hephaestin. *B,* Hepcidin is produced by the liver and secreted into the blood.
- o HFE protein, hemojuvelin (HJV), and transferrin receptor 2 (TFR2) may participate in the hepatic iron-sensing mechanism that regulates hepcidin expression.
- o Hepcidin reduces iron release by macrophages (and thereby increases macrophage iron stores)
- o Hepacidin also reduces iron absorption by duodenal enterocytes to reduce the amount of dietary iron in the circulation.
- o In *HFE*-related hereditary hemochromatosis, loss of functional HFE protein leads to aberrant hepatocellular sensing of plasma iron, inappropriately low levels of hepcidin, diminished macrophage iron stores, and greater duodenal iron absorption. MW, molecular weight.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 74-1, page 1241, Ninth Edition, 2010.
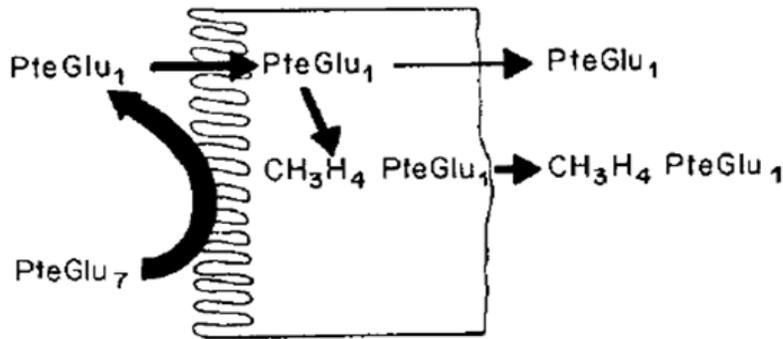
Figure 4. Proposed scheme of the digeston and absorption of dietary pteroylglutamates. Hydrolysis of polypteroylglutamates (shown here as PteGlu$_7$) probably occurs outside the intestinal epithelial cell. The overall rate of absorption into the mesenteric circulation is governed by the rate of transport of the monoglutamyl product (PteGlu$_1$). At physiologic doses, a substantial amount of PteGlu$_1$ is reduced and then methylated to CH$_3$H$_4$PteGlu$_1$ in the intestinal cell before release into the circulation.

Source: Rosenberg IH. Folate absorption and malabsorption. N Eng J Med 1975;293:1303.
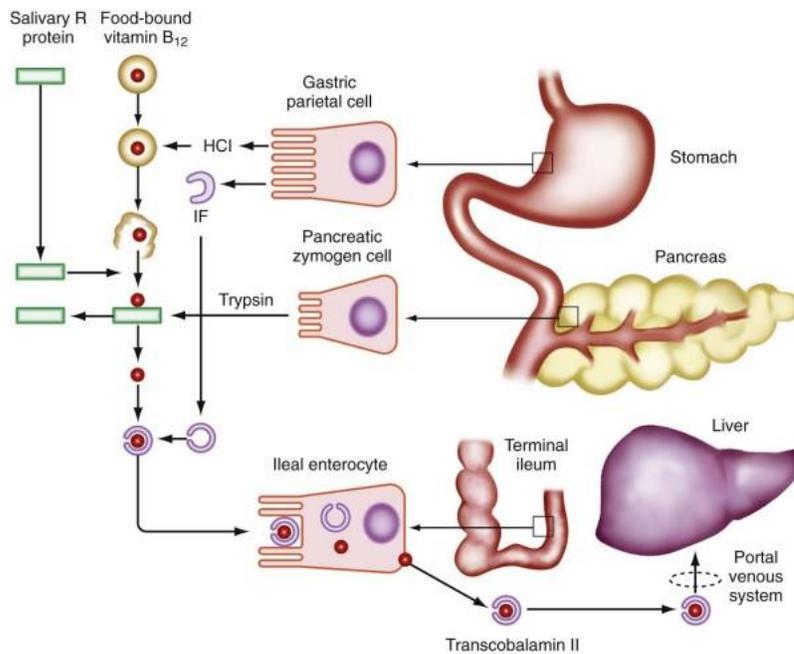
Figure 5. Absorption of Cbl (Cbl) requires proteolysis and intrinsic factor (IF).
  o The intrinsic factor secreted is far in excess of that needed for binding the available Cbl. protein derived from saliva is also present in great abundance.

- o   Cbl binds initially to R protein in the stomach at acid pH.
- o   Only after R protein is degraded by protease does Cbl bind to IF. After Cbl is absorbed in the ileum, it is bound to transCbl II (Kalser MH., 1985).

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-18, pg 1719, Ninth Edition, 2010.

Since transfer of Cbl from R protein to IF depends upon ambient pH, pancreatic insufficiency (with deficient bicarbonate production) or the Zollinger-Ellison syndrome (with excess HCl production) interferes with this process and may result in Cbl deficiency. Loss of the ileum from injury, disease (Crohn disease) or surgical reaction will result in Cbl malabsorption and deficiency. In the ileum, the IF-Cbl complex (but not free Cbl) binds to a BBM receptor, is absorbed, and in the cytosol of the ileocyte the Cbl is released from the IF. After trafficking across the enterocytes, Cbl is transported across the BLM and into the blood, bound to circulating proteins known as transCbls.

CALCIUM TRANSPORT ACROSS THE INTESTINAL EPITHELIUM
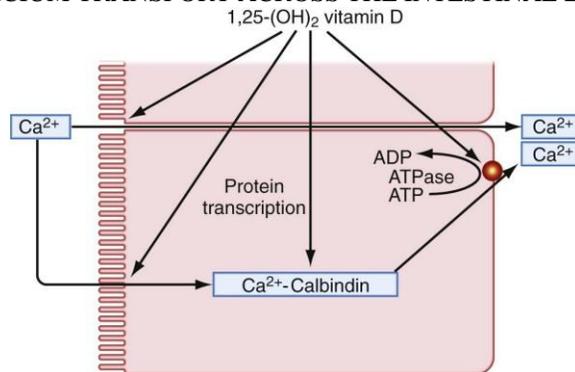
Figure 6. Mechanisms of. calcium transport across the intestinal epithelium
- o   A paracellular route allows bidirectional flux.
- o   Transport into the epithelial cell occurs via specific channels down an electrochemical gradient.
- o   A critical step is the binding to calbindin, which then presents calcium for export via a calcium-dependent adenosine triphosphatase (ATPase) on the basolateral membrane.
- o   Each of these processes appears to be influenced by 1,25-$(OH)_2$ vitamin D, although its maximal effect is on synthesis of fresh calbindin. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-20, pg 1719, Ninth Edition, 2010

Table 2. Comparison of Calcium and Magnesium absorption

	Calcium	Magnesium
• Site of Maximal Absorption	Duodenum, jejunum and proximal	Ileum
• Enhancing effect of 1, 25 (OH)$_2$ vitamin D on absorption:		
- Proximal	+	+
- Distal	+	-

3.2. Digestion and Absorption of Fat:

    The overall process of the digestion and absorption of fat, triglycerides, cholesterol, phospholipids and bile acids consists of five distinct phases, related to the respective functions of the stomach, pancreas, hepatobiliary, intestinal mucosa, and lymphatics (Figure 13 and 14 and Table 4). Physiologically, these involve (1) gastric emulsification of dietary triglyceride (TG) (2) pancreatic lipolysis of TG to fatty acid (FA) and monoglyceride (MG); (3) bile micellar solubilization of FA and MG with bile acids, as well as the synthesis of BA from cholesterol; (4) uptake into the enterocytes, with reesterification of the MG with FA to form TG, and chylomicron formation in the presence of cholesterol, cholesterol esters, phospholipids and protein; and delivery of chylomicrons in lymphatics to the body for utilization of fat.

    The average North American diet contains 60–100 g of fat each day, mostly in the form of neutral fat or triglycerides. The fat in masticated food is emulsified, and undergoes some lipolysis by gastric lipase. In the proximal intestine, TG comes under hydrolytic attack by pancreatic colipase and lipase, producing glycerol, FA and MG. Pancreatic lipase acts only at oil-water interfaces and requires a large surface area. Pancreatic colipase is required to achieve the necessary close contact of lipase with the triglyceride molecul*E. coli*pase is secreted as pro-colipase from the pancreas, followed by trypsin activation. Following the entry of food and particularly fat into the duodenum, cholecystokinin (CCK) is released from mucosal cells, causing gallbladder contraction.

Table 3. Key Steps in the Absorption of Lipids

➢ Stomach	o	Emulsification to increase the stability of lipid droplets
	o	Lipase breaks down TG to FA and DG; DG further enhances emulsification
➢ Pancreas and duodenal lumen	o	Further hydrolysis of TG by pancreatic lipase, further enhanced by biliary BS and lecithin
	o	In presence of colipase, the lipase moves closer to the emulsification droplet, closer to the hydrolytic sites of lipase
	o	At pH~7, lipolysis of FA from α, and α$_3$ position of TG, releasing MG+FA
	o	Dietary cholesterol is esterified. Pancreatic cholesterol esterase releases FA and cholesterol. These are absorbed, and re-esterified in the enterocyte cytosol.
➢ Hepatobil-iary Phase	o	BS and PL from bile enhance pancreatic hydrolysis, and AT BS concentrations above CMC, simple micelles are formed, solubilizing FA,

MG, FSV, and CHOL

- o Once the CMC of the BS has been reached, simples micelles form

- o Simple micelles incorporate FA, MG, PL and form mixed micelles

- o Mixed micelles act as a reservoir for the solubilized products of the digestion of dietary lipids, and aid their diffusion across the UWL.

➤ Enterocyte
- o Once the micelle has diffused across the UWL just external to the BBM, the lipid products solubilized in the micelle either dissociate from the lipophilic micelle into the lipophilic BBM, or the lipid components of the micelle dissociate from the micelle into an aqueous phase, and from there pass into and through the BBM.

- o The BS which were part of the micelles diffuse back to the bulk phase in the intestinal lumen, where they solubilize further luminal lipid, and shuttle it back once again to the BBM; very little BS is absorbed in the proximal intestine, allowing the BS concentration to remain above the CMC, and micelles to be formed and reformed to continuously optimize the solubilization of the lipolytic products.

- o The products of lipolysis (FA, MG) may diffuse across the lipolytic BBM, or may bind to the BBM lipid-binding proteins, CD36 or FATP

- o Only a tiny amount of glycerol is absorbed, to be later used to synthesize TG in the cytosol.LCFA may bind directly to a FATP dimer in the BBM, or may bind first to BBM CD 36 and then to the dimeric FATP.

- o Once the LCFA is in the enterocyte cytosol, it binds to LACS, ACBP or I-FABP/L-FABP

- o I-FABP binds LCFA, and L-FABP binds MG and LPC

- o LCFA initially bound to LACS is transferred to ACBP; ACBP and FABP prevent LCFA from diffusing back across the BBM and out of the enterocyte

- o ACBP and FABP also shuttle LCFA to the ER for the resynthesis of TG, modulating intracellular lipid metabolism by regulating gene expression.

- o In the enterocyte, most absorbed LPC is reacylated to form PC and a small amount is hydrolyzed to form glycerol-3-phosphorylcholine, which is transported in portal blood to the liver

- o SCP-1 is involved in the microsomal conversion of squalene to lanosterol. SCP-2 is both involved in the microstomal conversion of lanosterol to cholesterol, and the transport of cholesterol in lipid droplets to the mitochondria.

- o During fasting, intracellular enterocyte glucose is used to form α-glycerophosphate, Acyl CoA plus α-glycerophosphate form first phosphatidic acid and then PL+TG.

- o When adequate amounts of MG are present such as during a meal containing lipids, the MG pathway is active and inhibits the α-glycerophosphate pathway.

- o Microsomal acyl coA-lipase synthesize Acyl coA from FA,acyl coA plus MG form DG, and then TG, through what is known as the monoglyceride pathway. With feeding of fat in the SER, the FA is acetylated with CoA in the presence of ATP to form acyl coA

- o During the fed period, the monoglyceride pathway synthesizes about 96% of TG, whereas a tiny amount (~4%) of TG is formed during this absorptive period by acylation of the tiny amount of glycerol that is absorbed.

- o The TG and PL are synthesized in the SER. In the RER the apolipoproteins are synthesized.

- o CHOL in the enterocyte cytosol is from diet, biliary cholesterol, plasma lipoproteins, and newly synthesized cholesterol. The CHOL is esterified by ACAT and $ACAT_2$, and a lesser role by cholesterol esterase.

- o The chylomicrons pass to the Golgi apparatus, and then to the enterocyte BLM

- o The chylomicrons for vesicles with the BLM to move by exocytosis into the lacteals

- o The gaps in the endothelial cells widen, and the chylomicrons move in theportal circulation

- o Water soluble MCTs move from the enterocyte cytosol directly across the BLM, without the need for micellar solubilization, re-esterification, or chylomicrons

- o When dietary levels of CHOL are high, ACAT is stimulated

- o The RER apolipoproteins and the SER-synthesize TG, CHOL and PL ester from chylomicrons and VLDLs in the SER.The FA in the TG in chylomicrons are largely from the diet; the FA in the PL are used to form VLDLs. With feeding, chylomicrons predominate, whereas with fasting, VLDLs predominate

- o The apolipoproteins formed in the enterocyte SER coat the chylomicrons (TG, PL, CHOL ester). Apo B is synthesized in the enterocyte Golgi cisternae, and then moves to the RER, where it is important for the synthesis and secretion of chylomicrons

- o The lipid transfer activity of the microsomal triglyceride transfer protein initiates the addition of lipids (PL, TG) to the primordial chylomicron particle

Abbreviations

ACAT, acyl cholesterol acyl transferase
ACBP, acyl CoA binding protein
BS, bile salts
CHOL, cholesterol
CHOL, cholesterol
CMC, critical micellar concentration
DG, diglyceride
ER, endoplasmic reticulum
FA, fatty acid
FATP, fatty acid transport protein
FSV, fat soluble vitamin
I-FABP, intestinal(-type) fatty acid binding protein
LACS, long chain fatty acyl-CoA synthetase

LCFA, long-chain fatty acid
L-FABP, liver (-type) fatty acid binding protein
LPC, lyso phosphatidyl choline
LPC, lysophosphatidylcholine
MCT, medium-chain length triglycerides
MG, 2-monoglycerol
MG, monolgyceride
PC, phosphatidyl choline
PL, phospholipids (Lecithin)
RER, rough endoplasmic reticulum
SER, smooth endoplasmic reticulum
TG, triglyceride
UWL, unstirred water layer
VLDL, very-low-density lipoproteins
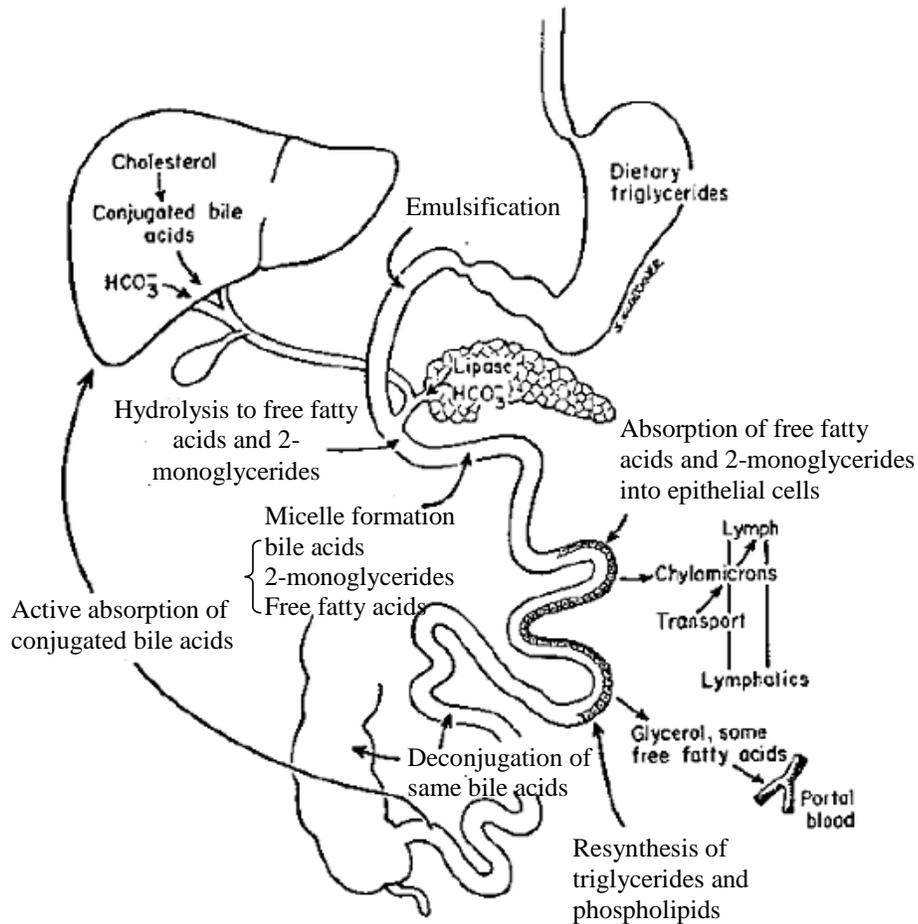
Figure 7. Diagram of the major steps in the digestion and absorption of dietary fat. These include (1) the lipolysis of dietary triglyceride (TG) by pancreatic enzymes; (2) micellar solubilization of the resulting long-chain fatty acids (FA) and β-monoglycerides (βMG; shown in figure as 2-monoglycerides) by bile acids secreted into the intestinal lumen by the liver; (3) absorption of the fatty acids and β-monoglycerides into the mucosal cell with subsequent re-esterification and formation of chylomicrons; and, finally, (4) movement of the chylomicrons from the mucosal cell into the intestinal lympathic system. During the process of chylomicron formation, small amounts of cholesterol ©, cholesterol ester (CE), and phospholipid (PL) as well as triglyceride are incorporated into this specific lipoprotein fraction.

Adapted from: Wilson FA, Dietschy JM. Differenital diagnostic approach to clinical problems of malabsorption. Gastroeneterology 1971; 61:912.
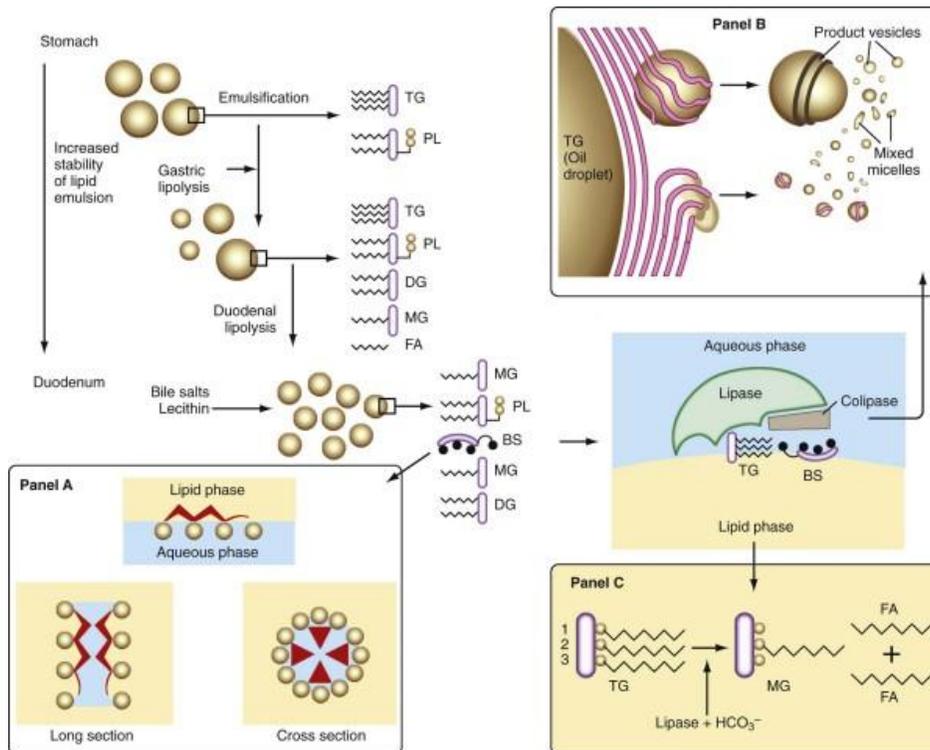
Figure 8. Steps in lipolysis.

- o The initial step in lipolysis is to increase the stability of the fatty emulsion.
- o Gastric lipase acts on triglycerides to yield fatty acids and diglyceride (diglyceride enhances emulsfication).

o This step is enhanced in the duodenum by bile salts and phospholipid (lecithin), which enable lipase, in the presence of colipase, to act at the surface of the emulsion droplet to bring it close to the triglyceride molecule, whereupon monoglyceride and fatty acids are released.

o Lipolysis in the duodenum yields fatty acids (from the α_1 and α_3 positions) and monoglyceride and occurs in a rapid and efficient manner at nearly neutral pH.

o In *panel A* are diagrammatic representations of bile salt molecules *(top)* oriented at an oil-water interface with its hydrophobic sterolic backbone in the oil phase and its hydrophylic hydroxyl and either taurine or glycine conjugates in the aqueous phase. At concentrations above critical micellar concentration, bile salts aggregate as simple micelles in water, with their hydrophylic groups facing into the water.

o Three hydroxyl groups (cholate) are shown as *open circles* and an additional polar group represents either taurine or glycine.

o *Panel B* is a diagrammatic sketch of the dispersion of the products of lipolysis into lamellae at the surface of the oil phase, each about 4 to 5 nm thick, with water spacings up to 8 nm, and from there into vesicles of about 20 to 130 nm in diameter.

o In *panel C,* fatty acids and monoglyceride within the vesicles pass into mixed micelles.

Abbreviations: BS, bile salt; DG, diglyceride; FA, fatty acid; MG, monoglyceride; PL, phospholipid; TG, triglyceride.

This article was published in *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Feldman M, Friedman LS, Brandt LJ., Ninth Edition, Elsevier, Philadelphia, 2010, Figure 100-4, page 1700.

The topic of the absorption of bile acids, including enterohepatic citculation of bile acids, is covered in the Liver chapter.

3.3. Digestion and Absorption of Carbohydrates

Starch present in wheat, rice and corn is a polysaccharide whose molecular weight ranges from 100,000 to greater than 1,000,000. The straight chain of glucose molecules in starch is bridged by an oxygen molecule between the first carbon (C1) of one glucose unit and the fourth carbon (C4) of its neighbor (α-1,4 glucose link). This type of starch is called amylose. Similar in structure to glycogen (the major form of polysaccharide in animals), it makes up as much as 20% of the starch in the diet. The glucose-to-glucose bridge is of the alpha type – in contrast to the beta type, which connects glucose units in cellulose, an indigestible saccharide. These non-starch polysaccharides provide most of the "unavailable carbohydrate" in the diet, mainly as dietary fibers, (e.g., cellulose and hemicelluloses). Cellulose is comprised of non digested β-1,4-linked glucose in straight chains, and hemicelluloses is comprised of polymers of pentose and hexose with straight as well as branched chains. While amylases cannot break down the β-1,4 bond, some digestion is caused by colonic bacteria, resulting in short chain fatty acids (SCFAs) which are absorbed and become a source of energy. Other dietary fibers such as pectins, gums and alginates that may

be partially hydrolyzed in the colon, while lignins are indigestible. Dietary fibers are active molecules that play an important role in altering the luminal content and mass, transit time and absorption of some nutrients.

The remaining 80% of the starch that humans ingest has a branch point every 25 molecules along the straight α-1,4 glucose chain. This starch is called amylopectin. These branches occur via an oxygen bridge between C6 of the glucose on the straight chain and C1 in the branched chain (α-1,6 branch points), which then continues as another α-1,4 glucose-linked straight chain (Figure 17).
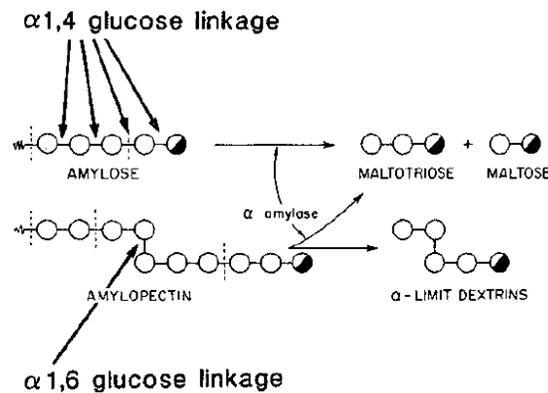
Figure 9. The action of pancreatic α-amylase on linear (amylose) and branched (amylopectin) starch. Circles indicate glucose residues and the reducing glucose unit.
Source: Gray GM. Mechanisms of digestion and absorption of food. In: Sleisenger MH, Fordtran JS (eds.), Gastrointestinal disease: pathophysiology, diagnosis, management. 3d ed. Philadelphia: WB Saunders, 1983:851.

Salivary and pancreatic α-amylases act on the interior α-1,4 glucose–glucose links of starch, but break down α-1,4 linkages close to a 1,6 branch point. Amylase proteins are encoded by a gene family on human chromosome 1 (i.e., AMY1 in the parotid gland, AMY2 in the pancreas). Salivary amylase acts in the mouth where slow chewing improves its action, while gastric acid leads to rapid inactivation of salivary amglose. Pancreatic amylase is the major enzyme of starch digestion and acts mainly within the intestinal lumen. The products of amylase digestion, are maltose and maltotriose. Since α- amylase cannot hydrolyze the 1,6 branching links and has relatively little specificity for 1,4 links adjacent to these branch points, large oligosaccharides containing five to nine glucose units and consisting of one or more 1,6 branching links are also produced by α-amylase action. These are called limit dextrins, and represent about 30% of amylopectin breakdown. The end products of amylase hydrolysis therefore are not single glucose molecules.

Digestion the oligosaccharides, (including α-limit dextrins) occurs with the BBM enterocyte hydrolytic enzymes (Figures 10 and 11). BBM carbohydrases (disaccharidases and oligosaccharidases) hydrolyze sugars containing two or more hexose units (Table 3). They are present in highest concentration at the villous tips in the jejunum, and persist throughout most of the ileum, but not in the colon. Lactase (Lactase-phlorizin hydrolase, LPH) breaks down lactose into glucose and galactose. Maltase-Glucoamylase differs from pancreatic α-amylase

since it sequentially removes a single glucose from the nonreducing end of a linear α-1,4 glucose chain, breaking down maltose into glucose.

| 1. Hydrolosis of complex CHO by pancreatic amylases | 2. Further hydrolysis of oligosaccharides by brush border enzymes | 3. Active transport of monosaccarides across the brush border | 4. Facilitated transport of monosaccarides into portal blood |

Starch ⟹ Oligosaccharides
Disaccharides ⟹ Monosaccharides ⇄ Monosaccharides ⟹ Portal Blood
Mucosal Cell
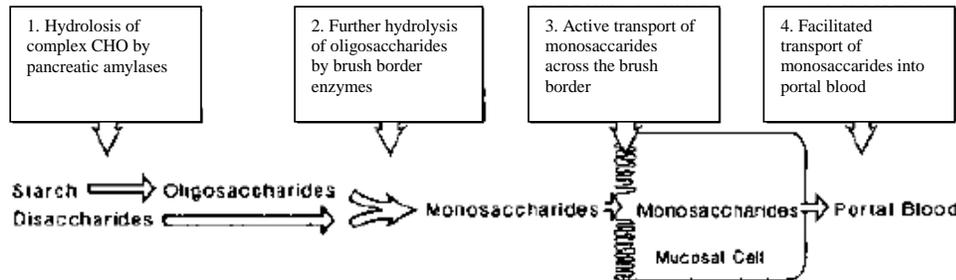
Figure 10. Major steps in the digestion and absorption of dietary carbohydrate.

Disaccharides ⟶ Monosaccharides

Microvilli (brush border)

Sucrose → Glucose
Lactose → Fructose
Maltose → Glucose
→ Galactose
→ Glucose
→ Glucose
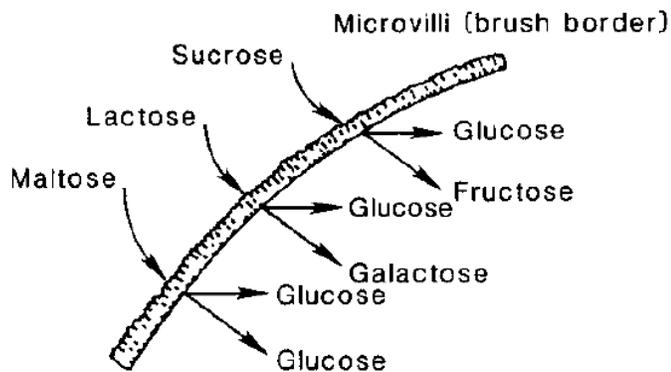
Figure 11. Disaccarides are split into monosaccarides at the brush border.

Sucrase-isomaltase is a hybrid molecule consisting of two enzymes – sucrase, hydrolyzing sucrose to glucose and sucrose and the other, α-1,6 branch points of the α-limit dextrins. Isomaltase, which is the debrancher enzyme, hydrolyzing the 1,6-glycosidic linkage of α-limit dextrins. Both enzymes, acting as sucrose-α-dextrinase, act on α-limit dextrin's α-1,4 link at the nonreducing end, yielding glucose. The sucrase moiety thus breaks down sucrose into glucose and fructose.

We are born with a full complement of BBM disaccharidases (Table 4). Intake of large amounts of sucrose or starch increases sucrase activity. Starvation reduces SI protein and activity, which are rapidly restored by refeeding. In contrast, increasing the dietary load does not up-regulate manipulation can regulate the activities of lactase or maltase. Disaccharidase enzymes are glycoproteins that are synthesized as proenzymes in the rough endoplasmic reticulum, then pass through the Golgi complex of the crypt and villus enterocytes for further processing. Lactase is completely processed when it is inserted into the BBM. Sucrase-isomaltase is inserted into the BBM, and is processed further by pancreatic proteases in the small intestinal lumen. In normal adult small intestine, these enzymes are expressed in the more well-differentiated villous cells compared to crypt cells and their activities are greater in the proximal compared to distal small intestine. Sucrase-isomaltase is encoded by a single gene located on chromosome 3 at locus 3q-25-26 while the lactase gene is located on the long arm of chromosome 2. Expression of SI depends upon steady-state levels of SI mRNA, as well as post-transcriptional and post-transcriptional regulation. Most regulation of LPH is by transcription.

Table 4. BBM carbohydrases

Enzyme	Substrate
➤ Lactase	• Lactose
➤ Maltase-glucoamylase	• α-1,4 linked oligosaccharides containing as many as 9 residues
➤ Trehalase	• Trehalose, α-limit dextrinase rapid hydrolysis of penta- and hexa-α-limit dextrins
➤ Sucrase-isomaltase (sucrase-α-dextrinase)	
- Sucrase	• Sucrose
- Isomaltase	• α-limit dextrin, α-1,6 link
- Both enzymes	• α-limit dextrin, α-1,6 link at nonreducing end

Once the disaccharides are broken down, the monosaccharides are absorbed. Glucose binds to the BBM carrier SGLT1, along with luminal Na^+. The gene for SGLT1 is on chromosome 22. A single missense mutation in amino acid 28 (aspartate → asparaginase) is responsible for familial glucose-galactose malabsorption. Normally, intracellular Na^+ concentration is low because of BLM Na^+, K^+-ATPase pumping Na^+ out of the enterocyte. Two molecules of Na^+ that entered the enterocyte with one molecule of glucose moves down its concentration gradient, across the cytosol to the BLM, to be pumped out by Na^+/ K^+-ATPase. The electrochemical gradient (PD) developed by Na^+ provides the driving force for glucose entry. This represents a secondary active transport process. Once the 2 Na^+ and 1 glucose molecule reach the cytosolic side of the BBM, glucose dissociates from the $SGLT_1$, then the 2 Na^+ come off the carrier.the ligand-free transporter changes its conformation, ready to again bind Na^+ and glucose in the intestinal lumen. This process is extremely rapid (turnover of $SGLT_1$ 1000 times a second at body temperature), and is responsible fo the daily absorption of about 5 L of water (for every two Na^+ cations and two anions, plus one

molecule of glucose, about 1100 molecules of water also cross the epithelium to maintain 150-osmolarity of the absorbate).

Fructose, released from the hydrolysis of sucrose, is transported by BBM GLUT5, a Na^+-independent carrier. Small amounts of glucose (and other sugars) may be metabolized in the enterocyte. Glucose and fructose exit across the BLM and into the portal system by the non–Na^+-dependent carrier, GLUT2.

In addition to $SGLT_1$ (high-glucose affinity Na^+-dependent, phlorizin-sensitive transporter), there is a low affinity transporter. This may be $SGLT_4$, $SGLT_6$, or $GLUT_2$. $GLUT_2$ may quickly traffic to and be inserted into the BBM during a glucose-containing meal, to further facilitate glucose and fructose, especially when there is a meal resulting in large amounts of these sugars. Primary lactase deficiency is very common in certain ethnic groups, such as persons from South East Asia, and may limit the intake of milk in some adults. Secondary Deficiency of disaccharidases results from anatomic injury of the small intestine, as in celiac disease, tropical sprue and gastroenteritis. When disaccharidase levels are sufficiently low, the particular oligosaccharide or disaccharide remains unhydrolyzed within the intestinal lumen, and augments intraluminal fluid accumulation by virtue of its osmotic effect.
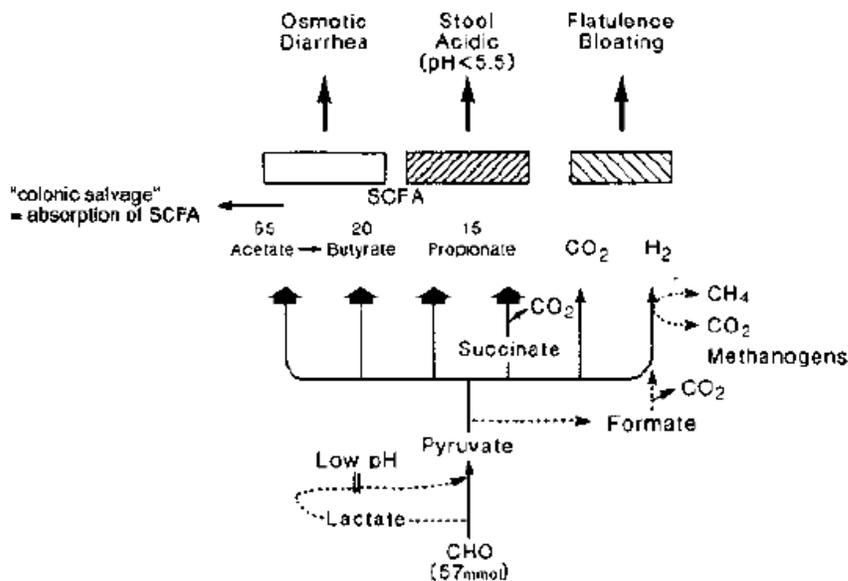
Figure 12. Intermediate and end products of anaerobic bacterial fermentation of carbohydrates. Minor pathways are depicted by dashed lines.

Source: Soergel KH. The role of the colon in case of inhibition of carbohydrate absorption. In: Creutzfeldt W, Fölsch UR (eds.), Delaying absorption as a therapeutic principle in metabolic diseases. Stuttgart and New York: Thieme Verlag, 1983:854.

Bacterial fermentation of disaccharides that reach the colon produces fatty acids, alcohols and gases (H2 and CO2) (Figure 12). The benefits of this bacterial fermentation to the host are twofold. First, reabsorption of fatty acids and alcohols in the colon "salvages"

calories from malabsorbed carbohydrates. Second, this colonic "salvage" reduces the number of osmoles of the solutes in the lumen, and hence lessens the water lost in feces.

Although infants have a relative deficiency of amylase, starch is not fed for the first few months of life. In the adult, there is a great excess of pancreatic amylase secreted into the intestinal lumen, so that even in patients with severe fat malabsorption due to pancreatic exocrine insufficiency, residual salivary and pancreatic amylase output are usually sufficient to completely hydrolyze starch by the time a meal reaches the mid-jejunum. Hence, severe maldigestion of starch rarely occurs in humans.

3.4. Digestion and Absorption of Peptides and Amino Acids Derived from Protein

An average adult consumes about 70 g of protein daily. About half of the protein in the intestine is derived from endogenous sources, such as salivary, gastric and pancreatobiliary secretions, desquamated mucosal cells and exudated plasma proteins.

Protein digestion is initiated in the stomach. Pepsinogen release from gastric chief cells is stimulated by gastrin, histamine and acetylcholine. Pepsins are derived from precursor pepsinogens; autoactivation of secreted pepsinogens in the acidic pH with loss of a small basic peptide, producing pepsin. Pepsin hydrolysis of proteins results in a peptide mixture with a small amount of amino acids (AAs). This mixture is emptied into the duodenum. Pancreatic amylase is secreted in an active form, but pancreatic proteases are secreted as proenzymes that require luminal activation. Enterokinase released from the enterocyte BBM converts trypsinogen to trypsin, in the duodenal lumen. Trypsin, in turn, activates other proteases, and autocatalyzes its own further activation from trypsinogen. Proteases have been classified into endopeptidases (trypsin, chymotrypsin, elastase), which split internal peptide bonds, or exopeptidases (carboxypeptidases A and B), which remove single AAs from the carboxyl-terminal end of peptides (Figure 3). The final products of luminal protein digestion consist of neutral and basic AAs (about 30%), as well as oligopeptides of 2 to 6 amino acids (about 70%).
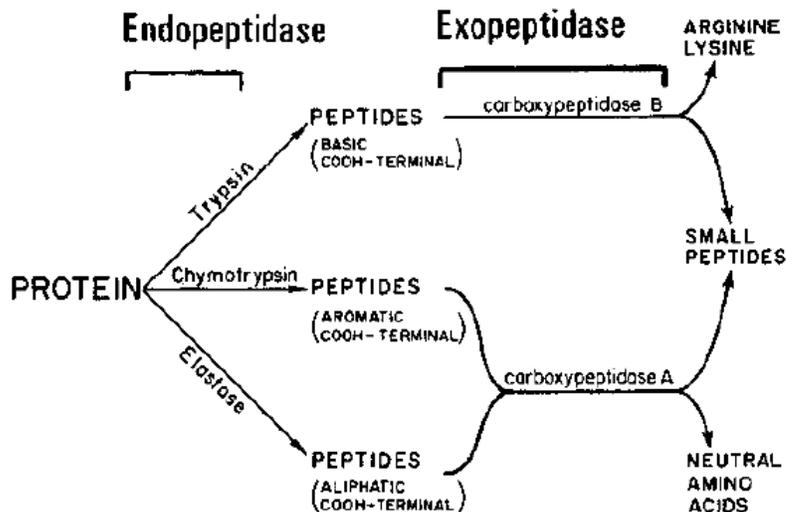
Figure 13. Sequence of events leading to hydrolysis of dietary protein by intraluminal proteases.

Source: Gray GM. Mechanisms of digestion and absorption of food. In: Sleisenger MH, Fordtran JS (eds.), Gastrointestinal disease: pathophysiology, diagnosis, management. 3d ed. Philadelphia: WB Saunders, 1983:854.

Peptidase activities are present in the enterocyte BBM and cytoplasm. Oligopeptides are hydrolyzed by BBM peptidases, but dipeptides and tripeptides are either hydrolyzed by the BBM or are absorbed intact and then hydrolyzed by the cytoplasmic peptidases. Most peptidases are aminopeptidases that remove an amino acid residue from the peptide amino terminus. Proline-specific carboxypeptidases and another dipeptidylaminopeptidase IV (DAP IV) have not been identified in the BBM and cytoplasm along with a cytoplasmic proline-specific enzyme. Most of the BBM peptidases are synthesized in the ER and Golgi complex, and are inserted in the BBM as glycoproteins.

Dipeptides, tripeptides and some tetrapeptides are absorbed intact into the enterocytes, AAs are more efficiently transported as peptides than as single amino acids, ie, there is a transport kinetic advantage of peptides over amino acids. Curiously, AAs in the duodenal lumen inhibits the hydrolysis of peptides (product inhibition), and the absorption of both amino acids and peptides is reduced by glucose and acid in the duodenal lumen. Because of this alternate small peptide pathway, patients with inherited basic or neutral aminoacidurias (e.g., cystinuria, Hartnup's disease) are able to absorb sufficient amino acids through intact peptide transport that protein deficiency states do not develop.

Adjacent to the BBM is an acid microclimate, which creates a BBM H^+ gradient. This is maintained by a BBM Na^+/H^+- exchanger and the BLM Na^+/H^+- ATPase. A single hydrogen ion is transported with peptide by a hydrogen-peptide cotransporter ($hPepT_1$). $hPepT_1$ transports neutral, anionic and cationic dipeptides. Note that $hPepT_1$ does not use a Na^+ electrochemical gradient, but rather the driving force achieved by a H^+-gradient: in the enterocyte cytosol, the H^+ is released from the $hPepT_1$-H^+ complex, and diffuses back across the BBM and into the lumen.The peptides transported by $hPepT_1$ are hydrolyzed by cytoclasmic peptidases. AAs absorbed primarily, by active carrier-mediated processes in the BBM. The L-isomers of the AAs are preferentially absorbed. Transport of AAs and rarely some peptides occurs across the BLM into the portal circulation.

There are 20 AAs and at least seven BBM four for neutral AAs, the NBB system, the PHE system for phenylalanine and methionine, the imino system for imino acids, and a fourth system for beta AA. There is a separate BBM transporter for basic and one for acidic AA, four BLM AA transporters. A small amount may be absorbed by passive diffusion, but most AA absorption is mediated by a Na^+-dependent gradient. SLC $36A_1$, aka the human PAT_1 (human proton-coupled amino acid transporter 1) in the BBM transports the imino acids proline and hydroxyproline as well as glycine, proline, alanine, taurine PAT_1, also uses a H^+ electrochemical gradient.

4. Absorption of Salt and Water

4.1. Passive Permeation

The epithelium of the small intestine exhibits a high passive permeability to salt and water that is a consequence of the leakiness of the tight junctions between epithelial cells. The ileum is less permeable to ions than is the jejunum, and the colon is even less permeable with

the reaction being "tighter" than the cecum. In the small intestine most water absorption occur as the result of carrier-mediated transport of solutes. Osmotic equilibration between plasma and lumen is rapid; as a result, large differences in ion concentration do not really develop. These intercellular junctions are more permeable to cations than anions, so that lumento-blood concentration differences for Na^+ and K^+ are generally smaller than those for Cl^- and HCO_3^-. One consequence of this lower passive ionic permeability (higher electrical resistance) is that electric potential differences across the colonic epithelium are an order of magnitude greater than those in the small intestine (remember Ohm's law, $E = IR$, where E is electrical potential, I is electrical current, and R is electrical resistance). Active Na^+ absorption, which is the main transport activity of the distal colon, generates a serosapositive charge or potential difference (PD). Under the influence of aldosterone (i.e., salt depletion), this PD can be 60 mV or even higher. A 60 mV PD will thus sustain a 10-fold concentration difference for a monovalent ion such as K^+. Most of the high K^+ concentration in the rectum is accounted for, therefore, by the PD.

Water and some small water-soluble solutes can pass across the mucosal barrier formed by the enterocytes. There are four types of structures in this paracellular pathway (Table 5).

Table 5. Composition and Function of Components of the Paracellular Pathway

Components of paracellular pathway	Membrane Proteins	Scaffolding Proteins	Function
ZO	Claudins JAMs Occludins	-ZO-1, ZO-2, ZO-3 -MUPP1	-influence charge-selectivity of TJs -vesicular transport via GTPase of the Ras superfamily -activation of molecules regulating PAR-3/-6 and a PKC -modify paracellular permeability
ZA	Cadherins (mostly E-) Catenins	-Actin cytoskeleton molecules; α-actinin, radixin, vinculin -Rab, SRC, yes	-cell-to-cell adherence -maintain cell polarity -intracellular signaling -changes in cadherins-catenins -may influence carcinogens
DES	Cadherin-like proteins	-Intermediate filaments -dense plaque of intracellular anchor proteins	
GJ	Connexins		-exchange of small molecules from one neighboring cell to another through connexin hemichannel

Abbreviations:

ZA, zona adherens	ZO-1, -2, -3, zona occludens proteins
ZO, zona occludens (aka Tight Junctions [TJs])	GTPase, guanosine triphosphatase
	PAR-3/-6, partition defective protein
DES, desmosome	aPKC, atypical protein kinase C
GJ, gap junction	
JAMs, junctional adhesional molecules	

Learning Points:
- Movement of an uncharged particle is determined by concentration gradients
- Movement of charged particles (ions) is determined by electrochemical gradients
- Permeability is higher and transepithelial resistance is lower in proximal versus distal intestine, and in the crypts versus than the villi
- The electrical potential inside the enterocyte is negative as compared with the outside, with the intracellular electronegativity creating a driving force more powerful than the chemical concentration gradient, e.g. Cl^- driven out of the cell by intracellular negativity, despite lower intracellular than extracellular concentration
- Water is absorbed largely in associating with the carrier-mediated absorption such as SGLT1 in the BBM, possibly by aquaporin membrane proteins in the small and large intestine, and by solvent drag across the paracellular pathway

---

4.2. Nutrient Dependent

$SGLT_1$ is high affinity, low capacity, whereas the $GLUT_2$ recruited to the BBM by a glucose containing meal ($SGLT_1$ activation, protein kinase activation) is low-affinity, high-capacity. $SGLT_1$ may also be a type of water channel, transporting 210 molecules of water with each 2 of Na^+ and 1 of glucose—the explanation for the effectiveness of ORS. Some water may also pass through the paracellular pathway: with transcellular glucose transport by $SGLT_1$, the actomyosin ring in the terminal web contracts, the transport of glucose across the BLM by $GLUT_2$ generates a small (3 mOsm) gradient, and water flows.

The BBM processes for nutrient absorption of glucose and neutral amino acids are Na^+-dependent. The sodium pump (Na^+/ K^+-ATPase), located in the BLM of the enterocyte, extrudes Na^+ that has entered the enterocyte from the lumen, thereby maintaining a low intracellular Na^+, a high intracellular K^+, and a negative intracellular PD. This Na^+/ K^+ pump provides the energy for uphill sugar and amino acid absorption across the BBM.

Glucose is cotransported with Na^+ by way of the BBM Na^+-dependant sugar transporter SGLT1 (Figure 14). Persons with intestinal secretory diseases such as cholera absorb glucose normally. Na^+ (and thus water) are also absorbed with glucose, so that the secretory fluid losses incurred by these patients can be replaced by oral glucose-electrolyte solutions (e.g.; ORT, oral replacement therapy). Intravenous fluids may therefore not be needed unless the patient is semiconscious, or too nauseated to drink the necessary large volumes of ORT to correct the dehydration arising from the diarrhea.
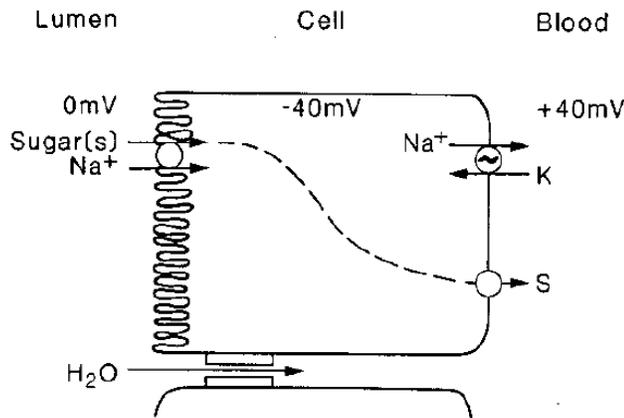
Figure 14. Na^+-coupled sugar absorption in the small intestine. This model presents the mechanism for sodium-coupled absorption of sugar. In addition to sugar, many amino acids, certain B vitamins and bile salts are absorbed through this mechanism. Sodium is taken up across the membrane in association with glucose (SGLT1) and exits by means of the basolateral sodium/potassium-ATPase. Glucose exits through a facilitated diffusion pathway in the basolateral membrane (GLUT2). Details of the model are described next.

4.3. Nutrient-Independent

Nutrient-independent active absorption of electrolytes and water by intestinal epithelial cells occurs through mechanisms located along the small and large intestine. All of these mechanisms have a requirement for luminal Na^+ and for BLM Na^+/ K^+-ATPase. In the distal colon (Figure 15), the BLM contains Na^+ channels. Na^+ entering through these channels is then extruded across the BLM by the Na^+/ K^+-ATPase pump. Aldosterone quickly increases the number of these BBM Na^+ channels, and more slowly increases the number of BLM Na^+/ K^+-ATPase pumps. As a result, Na^+ absorption is enhanced in the distal colon.

Chloride (Cl^-) is absorbed along with Na^+, and traverses the epithelium by both cellular and paracellular routes. The transcellular route involves a Cl^-/HCO_3^- exchanger in the BBM, and Cl^- channels in the BLM. Intracellular mediators such as cyclic AMP (cAMP) do not affect these Na^+ channels. Thus, patients with secretory diarrheas, who are salt-depleted and therefore have elevated blood levels of aldosterone, are able to reabsorb some of the secreted Na^+ and fluid.

In the more proximal colon and in the ileum, the luminal membrane contains $Na^+/H+$ exchangers (NHE) that permit net Na^+ entry (Figure 16). The colon and the ileum (but not the jejunum) also have Cl^-/HCO_3^- exchangers in their luminal membranes. The intracellular pH adjusts the relative rates of the anion and cation exchangers. Thus, H+ extrusion by Na^+/H^+ exchange results in cell alkalinization, which then stimulates Cl^- entry and HCO_3^- extrusion by the Cl^-/HCO_3^- exchange. The Cl^-/HCO_3^- exchanger then increases intracellular H^+, thereby sustaining further $Na^+/H+$ exchange.
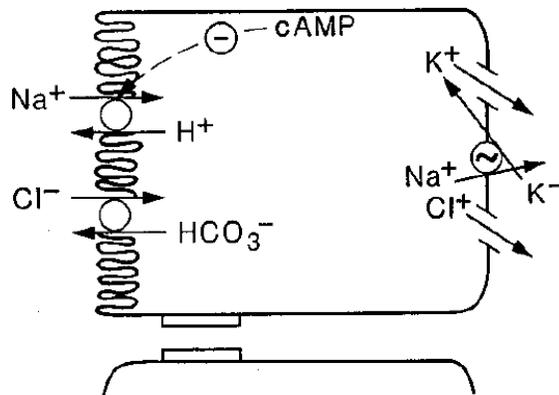
Figure 15. Electroneutral sodium chloride absorption in the small intestine and colon. Apical sodium chloride entry through sodium/hydrogen and chloride/bicarbonate permits sodium and chloride to enter the cell in an electroneutral fashion. Sodium exits the cell through the basolateral sodium/potassium-ATPase. The route of chloride efflux remains relatively speculative, but likely occurs through some basolateral channel.

Increases in cell concentrations of cAMP and free Ca^{2+} inhibit the Na^+/H^+ exchange. Cyclic AMP and its agonists thereby cause cell acidification, which in turn inhibits Cl–/HCO3 – exchange. Electrolyte absorption in the small intestine and proximal colon are down-regulated by hormones, neurotransmitters and some luminal substances (e.g. bacterial enterotoxins, bile salts, hydroxylated fatty acids) that increase cell concentrations of cAMP or free Ca2+. For this reason, body fluid secreted in response to these stimuli cannot be effectively reabsorbed in the absence of amino acids and sugars, except in the distal colon. In the jejunum, where there is no Cl–/HCO3 – exchange, $Na^+/H+$ exchange can be well sustained by anaerobic glycolysis, which generates H+ as well as some ATP.

4.4. Na^+-channel

The entry of Na^+ through the Na^+-specific channels (ENaCs) in the luminal membrane of the distal colon and rectum occurs down a Na^+ electrochemical gradient created by the Na^+-K^+ pump in the basal membrane. ENaCs are stimulated by increased synthesis by mineralocorticoids (aldosterone) and increased exocytosis by cAMP and vasopressin, and are inhibited by increases in the intracellular concentrations of calcium (iCa^{2+}). Aldosterone and cAMP also increase ENaCs by blocking the association of ENaCs with Nedd4-2, a ubiquitin protein ligase, which leads to the degradation of ENaCs: less Nedd4-2 assocaition, less breakdown of ENaC, more remaining ENaC activity (Figure 16).
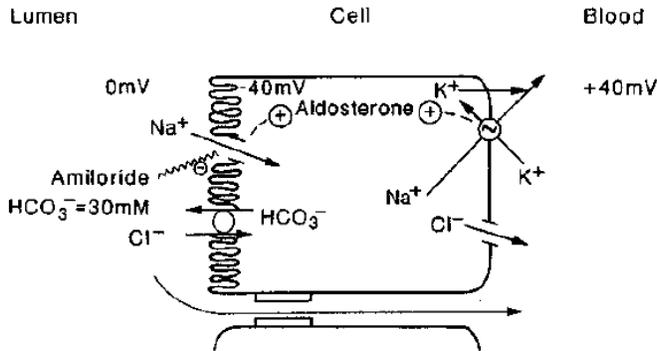
Figure 16. Electrogenic Na^+ absorption in the distal colon. Sodium enters the cell at the apical membrane through sodium channels and leaves the cell at the basolateral membrane through the sodium/potassium-ATPase. Details of the model are described in the text.

4.4.1. NHE, Na^+/H^+ exchangers

The modestly acidic intracellular environment (H^+-gradient) and the Na^+-gradient across the BBM created by the Na^+, K^+-ATPase in the BLM pumping Na^+ out of the cell, creates the conditions for the functioning of the sodium-hydrogen exchangers (NHE). This electroneutral process (exchange of Na^+ into and H^+ out of the cell) is more active during fasting than feeding. The NHE-1 is uniformly present along the villus-crypt unit (Figure) is on the BLM of the enterocytes and regulates intracellular pH, cell volume and growth. NHE-3 nad NHE-2 are on the apical membrane and mediate electroneutral Na^+ absorption in the small intestine, and NHE-2 is mainly in the proximal colon.

The 10 isoforms of NHE are modulated differently by endocrine, paracrine and neural stimulations and include NHERFs (NHE regulatory factors), kinases and phosphatises. For example, NHE-3 is upregulated by glucocorticoids acting through SGK_1, a serum and glucocorticoid inducible kinase. NHE-3 is doen-regulated by cAMP, through activation of protein kinase A, $NHERF_1$ and $NHERF_2$, and ezrin, a cytoskeleton protein. cGMP is also inhibitory of NHE-3.

4.4.2. Electrochemical NaCl absorption

Electroneutral NaCl absorption in the ileum and proximal colon is achieved through the coupling of Na^+ absorption to Cl^- absorption, through a Cl^-/HCO_3^- exchanger, Cl^- moving into the cell (giving electroneutral NaCl absorption), and HCO_3^- moving HCO_3^- out of the cell, to combine with H^+ to form H_2O. Cl^- also moves through the paracellular pathway in the jejunum, as the result of the transepithelial lumen PD-negative gradient.

4.4.3. Bicarbonate (HCO_3^-) transport

HCO_3^- is formed from intracellular metabolism, and cytoplasmic HCO_3^- also arises from diffusion of CO_2 into the enterocyte or colonocyte, or from the BLM Na^+/HCO_3^- cotransporter. HCO_3^- is secreted by electrogenic as well as by electroneutral processes. Electroneutral Cl^-/HCO_3^- exchange is the major process of HCO_3^- absorption, achieved by apical Cl^-/HCO_3^- exchangers. CFTR and other apical anion channels result in electrogenic secretion of HCO_3^-.

4.4.4. Chloride secretion and absorption

Water secretion is achieved by way of chloride (Cl⁻) secretion (Figure 17). The BLM NKCC1 transports 2Cl⁻, 1Na⁺ and 1 K⁺ into the secretory cell, such as the crypt enterocyte. The Na⁺ is pumped out of the cell by the BLM Na⁺ pump; the K⁺ leaves the cell through the BLM K⁺ channel. Na⁺ and H₂O cross through the paracellular pathway into the intestinal lumen, where the Cl⁻ channel combines with the paracellular pathway of Na⁺.
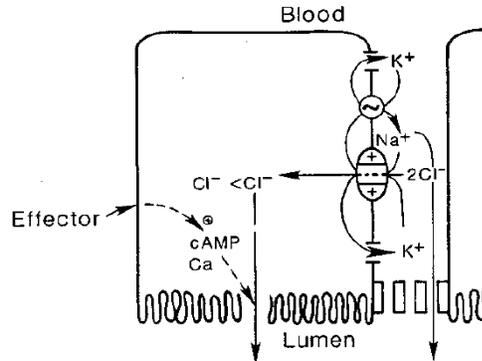
Figure 17. Electrogenic chloride secretion in both small and large intestine. A cyclic AMP-activated channel in the apical membrane permits hormone-stimulated chloride secretion. the chloride channel is coded by a gene (cystic fibrosis transmembrane conductance regulator [CFTR]) that is responsible for cystic fibrosis. Chloride enters the cell through a sodium/potassium transport along the basolateral surface. Details of this model are discussed in the text.

There are at least three classes of classes of Cl⁻ channels, the best known of which is CFTR. CFTR belongs to the ABC (ATP binding cassette) protein family. CFTR activity is increased by protein kinase A (PKA) activation of the R domain of CFTR, increasing gating and activity of the Cl⁻ channel, as well as recruiting the insertion of CFTR into the apical membranes. In persons suffering from cholera, the organism *Vibrio cholerae* produces several toxins which stimulate BLM adenyl cyclase, increase cytoplasmic cAMP, which stimulates secretion through the BBM Cl⁻ channel (CFTR), and reduces Na⁺ absorption. Drugs are being developed to inhibit or to stimulate CFTR, for purposes of treating diarrhea or constipation, respectively.

The calcium-activated Cl⁻ (CLCA) channels are Cl⁻ channels involved in rotavirus-associated diarrhea. Cl⁻ secretion across the BLM of the enterocytes is accomplished through the K⁺ channels, the cAMP-activated KCNE₃/KCNQ₁ channels and the Ca²⁺-calmodulin-activated KCNN4 channels.

4.4.5. Potassium (K⁺) transport

Despite the high fecal K⁺ level, little K⁺ is lost in the stool, since stool volume (about 200–300 mL per day) is normally so low. With high-volume diarrhea of small bowel origin, stool K⁺ loss is because of the large volumes involved. In such states, the stool K⁺ concentration is low (and the Na⁺ concentration relatively high) because diarrheal fluid passes through the colon too rapidly to equilibrate across the colonic epithelium.

The lumen-negative PD in the small intestine provides the driving force for passive K^+ absorption. The H^+, K^+-ATPase pumps in the luminal membrane of the distal large intestinal colonocytes actively transports K^+. Cl^- secretion across the BLM of the enterocytes is accomplished through the K^+ channels, the cAMP-activated $KCNE_3/KCNQ_1$ channels and the Ca^{2+}-calmodulin-activated KCNN4 channels.

4.5. Regulation of Electrolyte Absorption

Intestinal ion transport is regulated by luminal contents, autocrine factors, as well as by PINES, extracellular factors from Paracrine, Immunologic, Neural, and Endocrine Systems. There is integration of the ENS, GALT/MALT (Gut-Associated Lymphoid Tissue, and Mucosa-Associated Lymphoid Tissue), interneurons in the myenteric or submucosal plexuses, epithelial cells and blood vessels. There are agonists of electrolyte absorption (Table 6) and secretion (Table 7) and the balance between absorption and secretion determination the net absorption/ secretion.

Table 6. Agents that stimulate intestinal absorption of fluid and electrolytes

Endogenous Absorbtagogues	Pharmacologic agents
o α-Adrenergic agonists	o Berberine
o Aldosterone	o Clonidine (α_2-agonist)
o Angiotensin	o Cyclooxygenase inhibitors
o Enkephalins	o Glucocorticoids
o Glucocorticoids	o Lithium
o Growth hormone	o Mineralocorticoids
o Neuropeptide Y	o Octreotide
o Peptide YY	o Opiates
o Prolactin	o Propanolol
o Short-chain fatty acids	
o Somatostatin	o Octreotide

Table 7. Endogenous agonists of intestinal secretion and their intracellular mediators

Intracellular Mediator	Agonist
➢ Ca^{2+}	o Acetylcholine
	o Bombesin
	o Galanin
	o Gastrin
	o Histamine
	o Motilin
	o Neurotensin
	o Serotonin
	o Substance P

- ➢ cAMP
  - o Adenosine
  - o Arachidonic acid
  - o Bradykinin
  - o Peptic histidine isoleucine
  - o Platelet activating factor
  - o Prostaglandins
  - o Reactive oxygen metabolites
  - o Secretin
  - o Vasoactive intestinal polypeptide

- ➢ cGMP
  - o Atrial natriuretic peptide
  - o Guanylin
  - o Nitric oxide

- ➢ Miscellaneous
  - o Calcitonin, calcitonin gene-related peptide
  - o Gastric inhibitory polypeptide
  - o Leukotrienes

Table 8. Cells secreting endogenous agonists of intestinal secretion

- ➢ ENS
  - o Acetylcholine
  - o Calcitonin, calcitonin gene-related peptide
  - o Neurotensin
  - o Peptic histidine isoleucine
  - o Serotonin
  - o Substance P
  - o Vasoactive intestinal polypeptide

- ➢ Immune cells
  - o Adenosine
  - o Arachidonic acid
  - o Bradykinin
  - o Histamine
  - o Leukitrienes
  - o Motilin
  - o Nitric oxide
  - o Platelet activating factor
  - o Prostaglandins
  - o Reactive oxygen metabolites

- ➢ Endocrine cells
  - o Gastrin
  - o Motilin
  - o Secretin

- ➢ Mesenchymal cells
  - o Nitric oxide
  - o Prostaglandins

Abbreviation: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ENS, enteric nervous system.

Adapted from. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 99.2, page 1687, Ninth Edition, 2010.

4.6. Active Electrolyte Secretion Along the Intestine

In the secretory cell, the entry of Cl^- is coupled to that of Na^+ and probably also K^+ by a triple cotransporter with a stoichiometry of 1 Na^+, 1 K^+ and 2 Cl^-. Na^+ entering in this fashion is then recycled to the contraluminal solution by the Na^+/ K^+ exchange pump (Figure 17). K^+, diffuses back through K^+ channels.

Because of the Na^+ gradient, Cl– accumulates above the electrochemical equilibrium and can either 1) recycle back to the contraluminal side of the cell through the $Na^+/ K^+/2$ Cl– cotransporter, or through BLM Cl– channels, or 2) Cl- may be secreted into the lumen through luminal membrane Cl– channels. When Cl– is secreted into the lumen it generates a serosa-positive PD, which provides the driving force for Na^+ secretion through the paracellular pathway between cells. In the resting crypt secretory cell, the luminal Cl– channels are closed. Secretion is stimulated by opening the Cl– "gate" in the luminal membrane of the secretory cell.

There are numerous intracellular mediators of secretion such as cAMP, cGMP and Ca^{2+} (Tables 7 and 8). These arise from the blood, nerve endings, endocrine cells in the epithelium, mesenchymal elements (e.g. lymphocytes, plasma cells and mast cells), or the enterocytes themselves. Except for the cAMP agonists, lipoxygenase products and calcitonin, the actions of the other agonists are short-lived, desensitization develops rapidly, and they fine-tune electrolyte transport rather than invoking persistent secretion.

There are also agonists which inhibit secretion and/or stimulate absorption. These include adrenocorticosteroids, norepinephrine, somatostatin, enkephalins and dopamine. Glucocorticoids enhance electrolyte absorption throughout the intestinal tract, but the mechanisms involved are less well understood than for aldosterone. Steroids may act in part by inhibiting phospholipase A2 and therefore the arachidonic acid cascade. The adrenergic receptors on enterocytes are almost exclusively alpha 2 in type. The sympathetic nervous system in the intestinal mucosa releases norepinephrine (an alpha 2 antagonist) and so inhibits electrolyte secretion and stimulates absorption. Sympathectomy, whether chemical or surgical, leads to diarrhea. Diabetics with autonomic neuropathy sometimes develop persistent diarrhea that is associated with degeneration of adrenergic nerve fibers to the gut. An imbalance between the normal physiological levels of water and electrolyte absorption and secretion leads to diarrhea. This clinical topic is discussed in a later section.
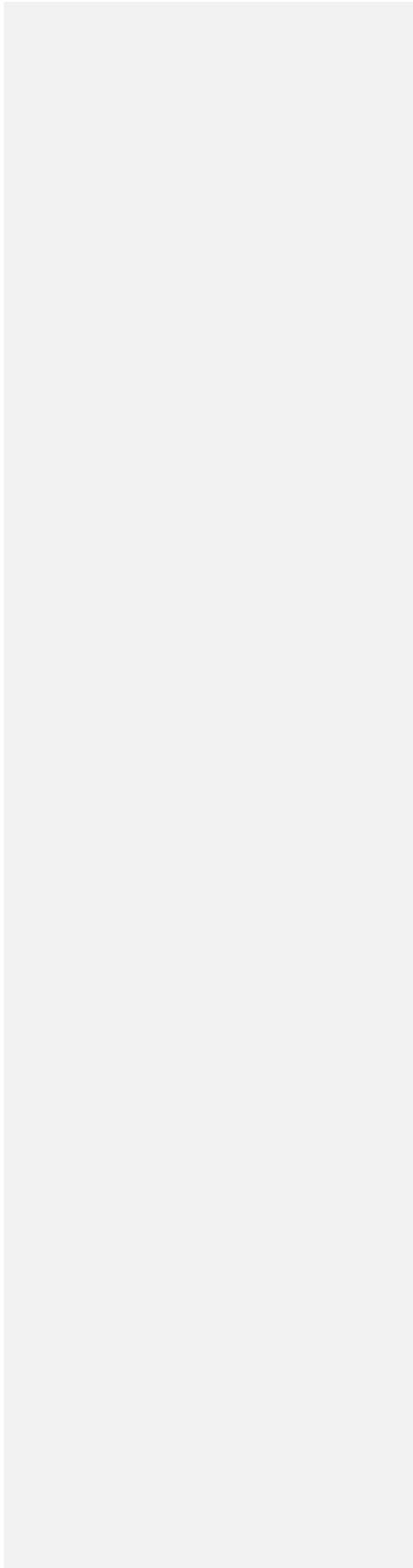
Chapter 7: The Small Intestine
Intestinal Digestion and Absorption in Disease
A.B.R. Thomson and H.J. Freeman

1. Malabsorption

1.1. Clinical Signs and Symptoms

There are numerous orders that cause malassimilation (Table 1). "Malabsorption" is the term that is usually used clinically to describe all processes that result in reduced delivery of nutrients to the portal circulation and/or lymphatics. "Malabsorption" in this context is strictly speaking not a correct term, since it may result from abnormal digestion or deranged enterocyte metabolism or delivery of nutrients is complex, so it is not surprising that many diseases may result in malabsorption. There are numerous signs and symptoms which may suggest the presence of malabsorption process or syndrome (Table 2), and this may lead to deficiencies of specific vitamins and minerals, leading to unique clinical manifestation (Table 3).

Table 1. Classification of malassimilation syndromes

Defective intraluminal digestion	Defective intramural absorption
o Mixing disorders	o Inadequate absorptive surface
o Postgastrectomy	o Intestinal resection or bypass
o Pancreatic insufficiency	o Mesenteric vascular disease with massive
o Primary	o intestinal resection
o Cystic fibrosis	o Regional enteritis with multiple bowel resections
o Secondary	o Jejunoileal bypass
o Chronic pancreatitis	o Mucosal absorptive defects
o Pancreatic carcinoma	o Biochemical or genetic abnormalities
o Pancreatic resection	o Celiac disease
o Reduced intestinal bile salt concentration	o Disaccharidase deficiency
o Liver disease	o Hypogammaglobulinemia
o Hepatocellular disease	o Abetalipoproteinemia
o Cholestasis (intrahepatic or extrahepatic)	o Hartnup disease
o Abnormal bacterial proliferation in the small bowel	o Cystinuria
o Afferent loop stasis	o Monosaccharide malabsorption
o Strictures	o Inflammatory or infiltrative disorders
o Fistulas	o Regional enteritis
o Blind loops	o Amyloidosis
o Multiple diverticula of the small bowel	o Scleroderma
o Hypomotility states (diabetes, scleroderma,	o Lymphoma
o intestinal pseudo-obstruction)	o Radiation enteritis
o Interrupted enterohepatic circulation of bile salts	o Eosinophilic enteritis
o Ileal resection	o Tropical sprue
o Ileal inflammatory disease (regional ileitis)	o Infectious enteritis (e.g., salmonellosis)
o Drugs (by sequestration or precipitation of bile salts)	o Collagenous sprue
o Neomycin	o Nonspecific ulcerative jejunitis
o Calcium carbonate	o Mastocytosis
o Cholestyramine	o Dermatologic disorders (e.g., dermatitis herpetiformis)
	o Lymphatic obstruction
	o Intestinal lymphangiectasia
	o Whipple's disease
	o Lymphoma

Table 2. Clinical signs and symptoms of malassimilation

- ➤ Clinical sign or symptom Deficient nutrient
  - o General Weight loss – calories
  - o Loss of appetite, amenorrhea - protein, energy
  - o Decreased libido – general malnutrition
  - o Skin Psoriasiform rash - zinc
  - o Eczematous scaling
  - o Pallor-Folate, iron, vitamin B12
  - o Follicular hyperkeratosis – vitamin A
  - o Perifollicular petechiae – vitamin C
  - o Flaking dermatitis – protein, energy, niacin, riboflavin, zinc deficiency
  - o Bruising – vitamin K
  - o Pigmentation changes – niacin, protein, energy
  - o Scrotal dermatosis – riboflavin
  - o Thickening and dryness of skin – linoleic acid
  - o Head Temporal muscle wasting – protein, energy
  - o Hair Sparse and thin: dyspigmentation – protein

  - o Night blindness – vitamin A
  - o Photophobia, blurring – riboflavin, vitamin A
  - o Corneal vascularization – riboflavin
  - o Xerosis, Bitot's spots – vitamin A, keratomalacia
  - o Mouth Glossitis – riboflavin, niacin, folic acid
  - o Bleeding gums – vitamin C, riboflavin
  - o Cheilosis – riboflavin
  - o Angular stomatitis – riboflavin, iron
  - o Hypogeusia – zinc
  - o Tongue fissuring – niacin
  - o Tongue atrophy – riboflavin, niacin, iron
  - o Scarlet and raw tongue – niacin
  - o Nasolabial seborrhea – pyridoxine
  - o Neck Goiter – iodine
  - o Parotid enlargement – protein
  - o Thorax Thoracic "rosary" – vitamin D

- ➤ Clinical sign or symptom Deficient nutrient
  - o Abdomen Diarrhea - niacin, folate, vitamin B12
  - o Distention – protein, energy
  - o Hepatomegaly – protein, energy
  - o Extremities Edema - protein, thiamine
  - o Softening of bone - vitamin D, calcium, phosphorus
  - o Bone tenderness - vitamin D
  - o Bone ache, joint pain - vitamin C
  - o Muscle wasting and weakness - protein, energy
  - o Muscle tenderness, muscle pain - thiamine
  - o Hyporeflexia - thiamine

  - o Nails Flattening, brittleness, luster loss, spooning - iron
  - o Transverse lines - protein
  - o Neurologic Tetany - calcium, magnesium
  - o Paresthesias - thiamine, vitamin B12
  - o Loss of reflexes, wrist drop - thiamine, foot drop
  - o Loss of vibratory and position, sense, ataxia - vitamin B12
  - o Dementia, disorientation - niacin
  - o Blood Anemia - iron, vitamin B12, folate
  - o Hemolysis - phosphorus

Carbohydrate malassimilation may result in excess flatus and the associated symptom of borborigmi distention or bloating. Malabsorbed carbohydrates that enter the colon are fermented by colonic bacteria to gases (CO_2, H_2 and CH_4) and organic acids. These organic acids produce

diarrhea by malassimilation. These gases produce flatulence, with associated borborygmi and abdominal distention. The presence of intraluminal H2 gas, eventually absorbed into the circulation and exhaled, forms the basis of the hydrogen breath test to detect carbohydrate malabsorption acting directly on colonic epithelium to stimulate fluid secretion and by their osmotic effect, which further draws water into the lumen. The presence of organic acids in the stool reduces the pH below 6 and suggests carbohydrate malabsorption.

Physical examination may reveal a distended tympanitic abdomen with hyperactive bowel sounds. Stools float on the water because of their increased gas content with severe malassimilation of carbohydrate there will be decreased plasma insulin levels, increased plasma glucagon and cortisol levels, and decreased peripheral T4-to-T3 conversion. The body may enter a state of oxidative metabolism, with catabolism of fat and muscle. There may be signs of weight loss from both fat stores and lean body mass. The patient will be weak and will easily develop fatigue. Fat loss will generally be noted as sunken cheeks and flat buttocks, with wrinkled or loose, skin indicative of loss of subcutaneous fat stores. The loss of muscle mass is easily noted as a reduction in the thenar mass and sunken soft tissues between the extensor tendons on the dorsum of the hands. There may be direct evidence of a reduced metabolic rate secondary to decreased T3 conversion. The patient may be mentally slowed.

Table 3. Specific vitamin and mineral deficiencies

Vitamin/mineral Clinical manifestation

- Vitamin A - Night blindness
  - Xerosis (dry bulbar conjunctiva)
  - Bitot's spots (conjunctiva plaques)
  - Keratomalacia (corneal ulceration)
  - Skin Hyperkeratosis

- Vitamin B12 - Anemia
  - Nonreversible loss of vibratory and position sense
  - Paresthesia
  - Gastrointestinal – diarrhea

- Vitamin C Skin - perifollicular papules (brittle hair)
  - Perifollicular hemorrhages
  - Gum bleeding
  - Skin purpura, ecchymosis

- Vitamin D - bone pain and softening
  - Joint pain
  - Rickets
  - Proximal myopathy

- Vitamin K - bruising
  - Bleeding

- Vitamin B6 - seborrheic dermatitis
  - (Pyridoxine) Cheilosis
  - Glossitis

- Niacin - dermatitis
  - Diarrhea
  - Dementia

- Thiamine - congestive heart failure
  - Wernicke's encephalopathy
  - Wernicke-Korsakoff syndrome

- Zinc - acrodermatitis enteropathica
  - Alopecia
  - Taste Hypogeusia

- Folate - anemia
  - Reversible loss of position and vibratory sense

Abbreviation: CVS = cardiovascular system; CNS = central nervous system

Excessive loss of fat in the stool deprives the body of calories and contributes to weight loss and malnutrition. More specific is the action of unabsorbed long-chain fatty acids, which act on the colonic mucosa to stimulate cAMP and to cause secretory diarrhea. In addition, fatty acids bind calcium, which would normally be available to bind oxalate. In fat malabsorption, oxalate is not bound to calcium and remains free (undissociated) within the colonic lumen, where it is readily absorbed. This results in oxaluria and calcium oxalate kidney stones. Failure to absorb the fat-soluble vitaminns A, D, E and K also results in a variety of symptoms. Vitamin K deficiency presents as subcutaneous, urinary, nasal, vaginal and gastrointestinal bleeding. Vitamin A deficiency results in follicular hyperkeratosis. Vitamin E deficiency leads to a progressive demyelination of the central nervous system. Malabsorption of vitamin D causes rickets and osteopenia.

Severe loss of body protein may occur before the development of any laboratory abnormalities, so that the patient at risk must be indentified early. Impaired protein synthesis from liver diseases and excessive protein loss in renal diseases can further aggravate protein deficiencies arising from malassimilation. Protein deficiency results in edema and diminished muscle mass. Since the immune system is dependent upon adequate proteins, protein deficiency can manifest as recurrent infections. Protein deficiency in children results in growth retardation, mental apathy and irritability, weakness and muscle atrophy, edema, hair loss, deformity of skeletal bone, anorexia, vomiting and diarrhea. Protein-calorie malnutrition is known as marasmus, whereas protein malnutrition by itself (with sufficient caloric intake) is known as kwashiorkor.

Hypochromic microcytic anemia characterizes iron deficiency. Since malassimilation may result in folate or B12 deficiency (producing megaloblastic red cells), the microcytosis of iron deficiency may be obscured with automated cell counters. A dimorphic picture may result from combined deficiencies. Rarely, these may be accompanied by pica and dysphagia. Pica originally referred to the eating of clay or soil; however, the commonest "pica" in North America is the eating of ice. Dysphagia may be due to the Plummer-Vinson (Paterson-Kelly) syndrome (with atrophic papillae of the tongue and postcricoid esophageal webs), and/or cheilosis (reddened lips with angular fissures, aka cheilitis or angular stomatitis). Palor, weakness, fatigue, dyspnea and edema also can occur. Examination often reveals pallor, an atrophic tongue and koilonychia (brittle, flat or spoon-shaped fingernails).

The clinical picture of cobolamin (vitamin B12) and folic acid deficiency includes palor, glossitis, megaloblastosis, and elevated serum lactate dehydrogenase (LDH). Subacute combined spinal cord degeneration occurs with severe cobolamin deficiency as well as dorsal column damage. Neurologic manifestations are not part of folic acid deficiency. Symmetrical paresthesias in the feet and fingers may occur with associated disturbances of vibration sense and proprioception, progressing to ataxia with subacute combined degeneration of the spinal cord

Impaired absorption of calcium, magnesium and vitamin D lead to bone pain, fractures, paresthesias and tetany. In latent tetany, the neuromuscular instability can be brought out by provocative tests such as Chvostek's and Trousseau's sign. Osteomalacia resulting from vitamin D deficiency principally affects the spine, rib cage and long bones with or without fractures (Milkman's fractures). A child with calcium or vitamin D malabsorption will present with classical rickets.

Hypomagnesemia may cause seizures and symptoms identical to those of hypocalcemia. In addition, hypomagnesemia may reduce the responsiveness of the parathyroids to calcium and impair parathyroid regulation of calcium homeostasis.

1.2. Diagnostic Approach to Malassimilation

A detailed history and physical examination (must always include DRE – digital rectal examination) may, in some instances, provide clue to the cause and further focus the clinical evaluation, for example the detection of dermatitis herpetiformis might suggest the closely linked disorder, celiac disease. Or, a history of repeated bouts of severe abdominal pain and weight loss in a chronic alcohol abuser might suggest chronic pancreatic insufficiency after repeated bouts of alcohol-induced pancreatitis.

Investigation includes blood, breath and stool tests, diagnostic imaging including upper and lower GI tract endoscopy with biopsies, as well as double balloon endoscopy, if available. Numerous imaging methods of the small bowel are available, including small bowel barium studies, CT or MRI enterography, and video capsule endoscopy.

A complete blood count may show a macrocytic or microcytic anemia. A peripheral blood smear may demonstrate microcytic cells (i.e., iron deficiency), changes suggestive of megaloblastosis with hypersegmented polymorphs (i.e., folate or vitamin B12 deficiency) or splenic hypofunction (i.e., Howell-Joly bodies from hyposlenism in celiac disease). Serum calcium, phosphorus and alkaline phosphatase (from bone origin) may suggest osteomalacia. Serum albumin may provide an index of the nutritional state and protein stores. A reduced serum carotene, (vitamin A) vitamin D, and prolonged INR or (International Normalized Ratio, vitamin K) indirectly suggest fat assimilation and clotting status (before a small intestinal biopsy). Body iron stores may be assessed from the measurement of serum iron, total iron binding capacity (TIBC) % saturation and ferritin concentration. Serology for anti-transglutaminase is both sensitive and specific to detect celiac disease as long as person does not have lgA deficiency. Serology is positive a small intestinal biopsy should be done to confirm the serological suspicion of celiac disease before treatment with a gluten free diet. A fasting blood sugar and TSH measurement will help exclude diabetes or thyroid disease. Dual Energy X-ray Absorptiometry (DEXA) bone scanning is useful to detect osteopenic bone disease. Serum vitamin B12, an index of body stores of vitamin B12, may be reduced owing to reduced intake, deficient production of intrinsic factor, abnormal luminal pH, pancreatic insufficiency, small intestinal bacterial overgrowth (SIBO) or impaired ileal absorption. Hydrogen breath tests after an oral load of a sugar such as lactase, glucose, fructose or sucrose helps to establish the presence of SIBO. Fecal studies help to exclude infectious or parasitic condition. A 72 hour stool collection performed after a 3 day dietary fat intake of 100 gm/day is sometimes necessary, and should include stool weight (2200g/day), fat, bile acids, and depending on the circumstance, stool electrolytes, osmolality, and laxatives such as Mg^{2+} and plenophthalein.

1.2.1. Site of defect therapy

The therapy for some specific maldigestion or malabsorption syndromes are detailed in Table 4 and representative doses of some nutritional therapies are noted in Table 4.

Table 4. Therapy of malassimillation syndromes.

Site of defect	Therapy
Pancreas	Enzyme supplements; insulin; dietary counseling; surgery for pancreatic duct obstruction or cancer
Hepatobiliary	Endoscopic therapy or surgery for obstruction of biliary tree

Site of defect	Therapy
Mucosa	Diet, such as gluten withdrawal or milk-free diet; nutrient supplements; 5-ASA compounds or steroids for Crohn disease; antibiotics for bacterial overgrowth or Whipple's disease
Lymphatics	Low-fat diet; medium-chain triglycerides (MCTs)

2. Diarrhea

The term *diarrhea* usually means a change in the frequency (>3/day is considered to be abnormal). In physiological terms, diarrhea is the increased secretion or decreased absorption of electrolytes or water, with stool weights exceeding 200 g/day (higher unless are seen normally in persons consuiming much more than the usual 30 g fibre/day). To the patient, diarrhea ia a change in the frequency and fluidity of their stools. Note that persons with IBS may have frequent watery stools, but usually there is no abnormality in electrolyte or water absorption/secretion. "Overflow diarrhea" may occur in the person with severe constipation or fecal impaction or fluid-nature of the stools. Finally, disease of the distal colon or rectum can lead to loss of stool reservoir, with frequent and often painful passage of small stools, yet there may be little fecal water and no increase in stool weight.

If the diarrhea has lasted less than two weeks, the diarrhea is said to be "acute" probably has an infectious or toxic cause. When diarrhea lasts for longer than two weeks, other explanations need to be considered. In the absence of prior gastric surgery, the most common causes of chronic diarrhea in persons less than 50 years are the irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), chronic intake of diarrhea-causing drugs or alcohol, chronic intestinal infections such as giardiasis. In a person over the age of 50 years, and certainly if there is blood in the stools, colorectal cancer and fecal impaction with overflow diarrhea must always be appropriately excluded.

A sense of incomplete evacuation suggests involvement of the rectum or sigmoid colon. The passage of blood, pus and mucus suggests bowel inflammation, ischemic bowel disease or neoplastic diseases, including cancer. Malassimilation syndromes (discussed in the previous section) are suspect if there is passage of food and oil droplets, or if the patient develops symptoms suggestive of nutrient deficiency, particularly weight loss.

Understanding of the pathophysiology of diarrhea requires an appreciation of the normal balance between the processes of water and electrolyte absorption and secretion.

2.1. Investigation

For a patient with chronic diarrhea, a careful history and physical examination helps define the responsible site in the intestinal tract (Table 5). Although there is considerable symptom overlap, it may be possible to differentiate clinically a small intestinal cause of diarrhea from a colonic cause for diarrhea. Colorectal disease often is associated with small, frequent bloody motions accompanied by tenesmus and urgency. Small intestinal or pancreatic diseases often produce large volume, loose, pale and bulky stools that are uncommonly bloody or accompanied by urgency. Despite overlap, this "bedside" definition of the characteristics of the diarrhea may be helpful to avoid a less productive "shotgun" approach to the investigation.

Table 5. Simplified Clinical Approach to the Patient with Chronic Diarrhea
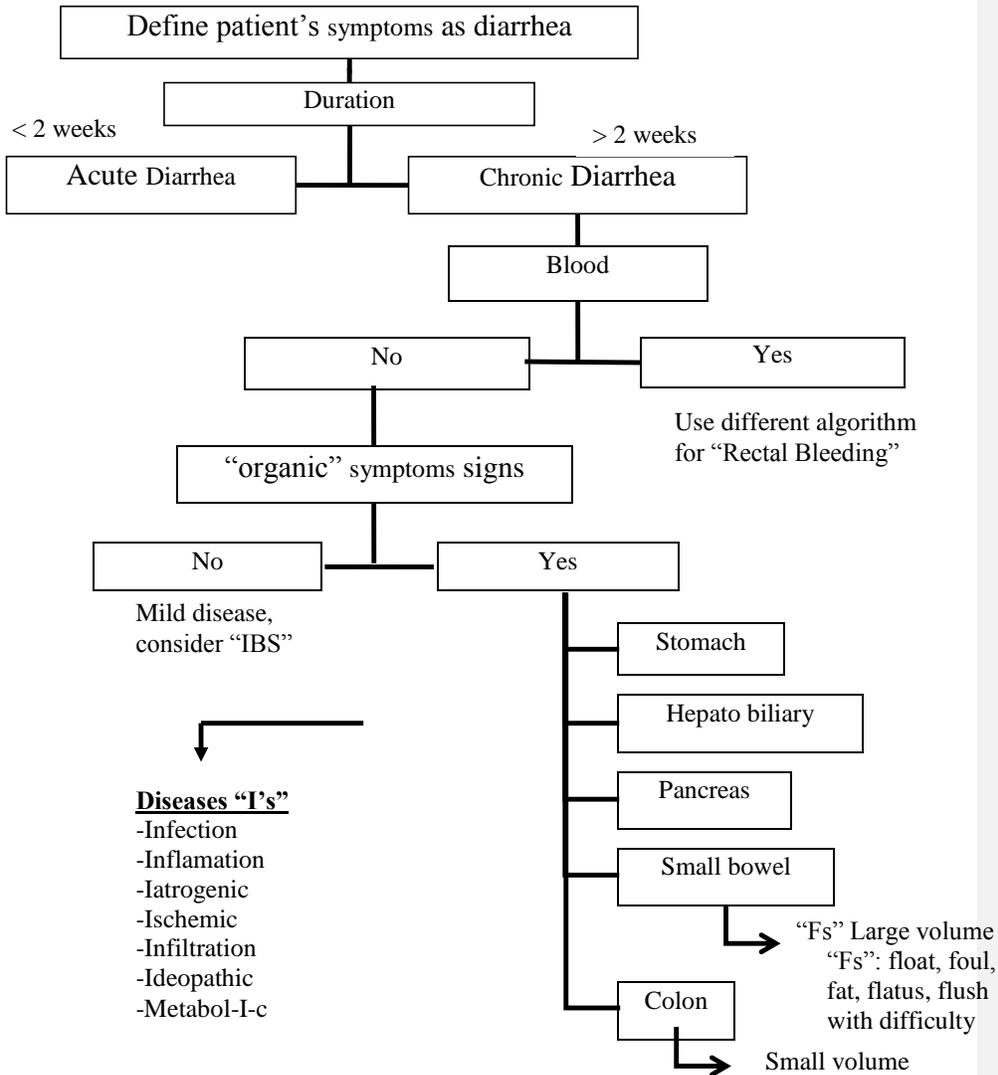
Because of the complexity of the mechanisms leading to chronic diarrhea, and the large number of causes, and often multiple interacting causes, it is useful to have a simple clinical approach to guide clinical thinking (Table 5 and 6) and investigations (Table 6). This may be a friendly way to approach the patient's problem, and then once a cause of chronic diarrhea is established (such as Crohn disease), then to apply your understanding of physiology to better understand the mechanisms causing diarrhea in that patient with that disorder.

Table 6. Simplified Approach to the Investigation of the Patient with Diarrhea

- o Blood   - CBC, ESR/CRP, lytes
  - Fe, FA, B_{12}, VA, VD, INR
  - Anti-tissue transglutaminase (tTG), IgA
- o Stool   - C/S, O/P, FOB
  - 72 hr collection (weight, fat, bile acids, osmololity, electrolytes)
  - Laxatives
- o Breath   - CHO : Lactose, Lactulose, Fructose, Sucrose
  - C 13/14 bile acid breath test
- o Diagnostic Imaging   - endoscopy + biopsy : EGD/colonoscopy/capsule endoscopy
  - SB barium, enteroclysis
  - Air contrast barium enema
  - CT or MR enterography

Table 7. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes

Minerals - Calcium PO: requires at least 1,000 mg elemental calcium daily as:
- Calcium gluconate (93 mg Ca2+/500 mg tablet)
- Calcium carbonate (200 mg Ca2+/500 mg tablet)

- IV: Calcium gluconate, 10 mL (9.3 mg Ca2+/mL) of 10% soln over 5 min
- Magnesium PO: Magnesium gluconate (29 mg Mg2+/500 mg tablet), 2–6 g/day
- IV: Magnesium sulfate (50% soln, 1 mL contains 2.03 mmol Mg2+)
- Iron PO: Ferrous fumarate (65 mg elemental Fe/200 mg tablet), 200 mg tid
  - Ferrous gluconate (35 mg elemental Fe/300 mg tablet), 600 mg tid
  - Ferrous sulfate (60 mg elemental Fe/300 mg tablet), 300 mg tid
- IM: Iron dextran 1 mL once daily (calculated from existing Hb)*
- IV: Iron dextran approx. 30 mL (calculated from existing Hb)* in 500 cc
- 5% D/W over 4 hrs, beginning with slow observed infusion

*NOTE: IM/IV Fe for deficit replacement only

- Zinc PO: Zinc sulfate (89 mg elemental zinc/220 mg capsule), 220 mg tid

Vitamins - Vitamin A Water-miscible vitamin A (25,000 IU/capsule), 25,000 IU daily
- Vitamin B12 100 μg/IM monthly
- Vitamin D2 (Ergocalciferol) (50,000 IU/capsule), 50,000 IU 3 times per week
- Vitamin E Water-miscible vitamin E (100 IU/capsule), 400 IU daily
- Vitamin K1 (Phytonadione) has caused fatal reactions, thus should be avoided
- Vitamin K3 (Menadione) water-soluble
  - PO: 5–10 mg/day
  - IV: 5–10 mg/day
- Folic acid PO: 1 mg/day
- Other : water-soluble Multiple vitamin 1/day

Table 8. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes (cont'd)

Pancreatic supplements
Enzyme activity (IU/unit)
Preparation Type Lipase Trypsin Proteolytic Amylase
Ku-Zyme HP® Capsule 2,330 3,082 6,090 594,048
Festal® Enteric-coated 2,073 ,488 1,800 219,200
Cotazym® Capsule 2,014 2,797 5,840 499,200
Viokase® Tablet 1,636 1,828 ,440 277,333
Pancrease® Microencapsulated
> 4,000 > 25,000

Usually taken as 4–8 capsules with each meal and half that number with snacks. Some patients will need higher doses or will need acid-lowering therapy with an H2-receptor antagonist or a proton pump inhibitor to alkalize the fluid in the duodenum and achieve greater activity of the pancreatic enzymes.

➢ *Bile salt binding agents* Precision

Cholestyramine 4 g (1 scoop), 3–6 times daily, according to response — Isotonic Diet® ,960 29 800 ,960 300
Precision LR Diet® 1,110 26 700 ,810 525
Psyllium and aluminum hydroxide gel may also be effective — Travasorb STD®
(unflavored) 1,000 45 920 1,170 450
Colestipol 1 g 3–6 times daily, according to response — Standard Vivonex®
(unflavored) 1,000 21 470 1,170 550
➢ *Caloric supplements* — High-Nitrogen
Medium-chain triglyceride oil: (8 cal/mL), 60 mL/day po, 480 cal/day — Vivonex®
(unflavored) 1,000 44 530 1,170 810
Portagen®: medium-chain triglyceride + other oils: (1 cal/mL), 1 L/day — Meritene Powder®
in milk 1,065 69 1,000 3,000 690
Enteral supplements: — Compleat B® 1,000 40 1,200 1,300 390
Grams of Osmolality — Formula 2® 1,000 38 ,600 1,760 435–510
Kcal/ protein/ Na K mOsm/kg* — *When prepared in standard dilution
Product 1,000 mL 1,000 mL mg/L mg/L Water — Parenteral supplements: Intralipid® 1 L/day IV
Ensure® 1,060 37 740 1,270 450 — (10 mL/kg/day)
Isocal® 1,040 34 530 1,320 300 — Travasol® 2 L/day IV (mix as per patient's
Osmolite® 1,060 37 540 1,060 300 — protein requirement)

2. Acute Diarrhea
2.2.1. Bacterial Diarrhea

Three major clinical syndromes caused by bacterial infections are 1) food poisoning, 2) infectious gastroenteritis and 3) traveler's diarrhea (Table 9).

In immunocompetent individuals, enteric infections are usually self-limiting and resolve in less than two weeks. Acute infections diarrheas are classified into *toxigenic types*, in which an enterotoxin is the pathogenic mechanism, and *invasive types*, in which the organism penetrates

the enterocyte or colonocyte as primary event (although an enterotoxin may be produced as well). Enterotoxins are either *cytotonic* (producing intestinal fluid secretion by activation of intracellular enzymes, without damage to the epithelial surface) or *cytotoxic* (causing injury to the enterocyte as well as inducing fluid secretion).

2.2.2. Food Poisoning

The food poisoning syndrome characteristically features the development of a brief but explosive diarrheal illness in persons following exposure to a common food such as a restaurant meal or family picnic is suggestive. Food source may be contaminated with bacteria or bacterial toxins; such as *Staphylococcus aureus*, or Salmonella species. The diagnosis of food poisoning is usually made by history. Except in special circumstances (e.g., botulism), isolation of the toxin is not cost-effective.

Table 9. Common causes of acute diarrhea

Drugs Bacteria (toxin-mediated, cytotoxic)	Viruses
Laxatives Clostridium difficile	Bacteria (toxin-mediated, cytotoxic)
Antacids Staphylococcus aureus	Parvovirus (Norwalk agent)
Antibiotics Shigella dysenteriae	Enterotoxigenic Escherichia coli Reovirus
Cholinergic drugs Campylobacter jejuni	(rotavirus)
Lactose Yersinia enterocolitica	(both heat-labile and heatstable
Guanethidine	toxins) Protozoa
Quinidine	*Vibrio cholerae*e Cryptosporidia
Bacteria (invasive)	Vibrio parahaemolyticus Giardia lamblia
Digitalis Salmonella	Clostridium perfringens Entamoeba histolytica
Colchicine	Bacillus cereus
Enteroinvasive Escherichia coli	Parasites
Potassium supplements	Strongyloides
Lactulose Bacteria (unknown mechanism)	Trichuris
Enteropathogenic Escherichia coli	
Enteroadherent Escherichia coli	

Salmonella food poisoning has been attributed to an enterotoxin similar to that of *Staphylococcus aureus*, but none has been clearly identified. Within 12 to 36 hours after ingestion of contaminated foods (usually poultry products), there is a sudden onset of headaches, chills and abdominal pain, with nausea, vomiting and diarrhea. These symptoms may persist for one to four days before subsiding. Antibiotic therapy of non-typhoidal Salmonella gastroenteritis fails to alter the rate of clinical recovery. In fact, antibiotic therapy will increase the duration of intestinal carriage of the Salmonella, and is contraindicated.

Certain conditions increase the risk of salmonellosis: hemolytic anemia, malignancy, immunosuppression, achlorhydria and ulcerative colitis. With uncomplicated Salmonella gastroenteritis, treatment is symptomatic. In fact, antibiotic therapy increases the duration of intestinal carriage of these organisms. Patients with complicated Salmonella gastroenteritis (e.g., those with predisposing conditions or sepsis, or who are very young or very old) should be treated with ampicillin or co-trimoxazole.

o *Campylobacter jejuni*–induced diarrhea is more common than diarrhea from either

Salmonella or Shigella. Infection is from consumption of improperly cooked or contaminated foodstuffs. Campylobacter attaches to the mucosa and releases an enterotoxin that destroys the surrounding epithelia. Clinically, there is often a prodrome of constitutional symptoms along with headache and generalized malaise. A prolonged diarrheal illness follows – often with a biphasic character, with initial bloody diarrhea, slight improvement, then increasing severity. The illness usually lasts less than one week, although symptoms can persist for a longer period, and relapses occur in as many as 25% of patients. Erythromycin 500 mg q.i.d. for 7 days is optimal therapy.

o *Clostridium perfringens* and *Bacillus cereus* are responsible for 90% of these outbreaks.

Symptoms usually reside with 24 hours, antibiotic therapy is not recommended. Oral rehydration therapy is usually possible. *Staphylococcus aureus* produces a heat-stable, odorless and tasteless enterotoxin that is generated in poorly refrigerated desserts and seafoods. Ingestion of the preformed enterotoxin causes nausea, vomiting and profuse diarrhea within 4 to 8 hours. Spontaneous resolution occurs within 24 hours. No specific therapy is available or necessary. *Clostridium perfringens* produces a preformed toxin from spores that germinate in contaminated meats cooked at less than 50°C. Symptoms are diarrhea and crampy abdominal pain without vomiting, beginning 8 to 24 hours after the meal.

o *Bacillus cereus*

Bacillus cereus produces either a diarrheal syndrome or a vomiting syndrome, depending upon the enterotoxin. The vomiting syndrome is always associated with ingestion of rice and is caused by a preformed toxin that is elaborated when rice is left to cool unrefrigerated. Flash-frying later does not generate enough heat to destroy the toxin. The diarrheal syndrome occurs after ingestion of the organism itself.

2.2.3. Infectious Gastroenteritis

The organisms responsible for bacterial gastroenteritis exert their predominant effects by invading and destroying the intestinal epithelium or by producing various enterotoxins.

o *Toxin-mediated, cytotoxic bacterial gastroenteritis*

- *Vibrio choleraiae* is the prototypic cause of toxigenic diarrhea. The *Vibrio cholerae* organisms elaborate a toxin that attaches to the inner cell membrane of the small intestinal BBM. Adenylate cyclase (aka "adenyl cyclase") elevates cyclic AMP (cAMP) levels. Cyclic AMP then stimulates the enterocyte to secrete fluid and electrolytes while at the same time impairing their absorption. Stool output can exceed 1 L/hour. Treatment is based on restoring fluid and electrolyte balance and maintaining intravascular volume. Even though fluid and electrolyte transport is impaired, glucose transport is intact. Since glucose absorption carries Na^+ (and thus water with it), an oral rehydration solution containing glucose, sodium and water will enhance water absorption during the profound dehydration stage of cholera ORT (oral hydration therapy) is sufficient for many sufferers.

Several types of *Escherichia coli (E. coli)* are intestinal pathogens. Each exerts its effects through different mechanisms (Table 10). Invasive forms of *E. coli* may cause colitis that may resemble ischemia bowel diease. *Enterotoxigenic E. coli* (ETEC) colonizes the upper small intestine after passing through the acid in the stomach, and bind to the mucosal surface without

penetrating into the cell. Two types of enterotoxins are produced by ETEC: the heat-labile toxin (also called "labile toxin" or LT) and the heat stable toxin (also called "stable toxin" or ST). ETEC can elaborate LT only, ST only, or both toxins. ST produces diarrhea by stimulating intestinal secretion through guanylate cyclase and subsequently cyclic GMP. LT produces diarrhea through adenylate cyclase and cyclic AMP. After a 24- to 48-hour incubation period, the disease begins with upper abdominal pain followed by watery diarrhea. The infection can be mild or severe. Treatment is symptomatic. Antibiotic therapy is not uised because it is ineffective, and also because the use of antibiotics may lead to the emergence of resistant ETEC strains.

Table 10. Types of Escherichia coli intestinal pathogens

o Toxin	o Mechanism
- Enteropathogenic Shiga-like toxin	- Adherence
- Enterotoxigenic Labile toxin (LT)	- Activates adenylate cyclase
- Stable toxin	- Activates guanylate cyclase
- Enteroinvasive Shiga-like toxin	- Penetrates epithelium
- Enteroadherent	- Adherence
- Enterohemorrhagic Shiga-like toxin (verotoxin)	- Unknown

- *Vibrio parahaemolyticus* causes acute diarrheal disease after consumption of seafood: raw fish or shellfish often without proper refrigeration. Explosive, watery diarrhea is the cardinal manifestation, along with abdominal cramps, nausea and vomiting. Fever and chills occur in 25% of cases. The duration of illness is short, with a median of three days. Treatment is symptomatic; there is no role for antimicrobial therapy.

After ingestion, *Shigella dysenteriae* organisms attack the colon, sparing the stomach and small bowel. Shigella organisms adhere to and then, penetrate the mucosal surface, multiply within the epithelial cells, moving laterally through the cytoplasm to adjacent cells by filopodium-like protrusions. Shigella organisms rarely penetrate below the intestinal mucosa, and almost never invade the bloodstream. Both attached and intracellular organisms elaborate toxic products. Even a small inoculum of 200 organisms (as contrasted with Salmonella, which requires greater than 107 organisms) will lead to crampy abdominal pain, rectal burning, fever, multiple small-volume bloody mucoid bowel movements. Intestinal complications include perforation and severe protein loss. Extraintestinal complications include respiratory symptoms, meningismus, seizures, the hemolytic uremic syndrome, arthritis and rashes. The treatment of choice is Ampicillin 500 mg q.i.d. or co-trimoxazole 2 tablets b.i.d. for 5 days.

- *Yersinia enterocolitica* is transmitted to humans from pets or food sources. It has become more readily detected in fecal specimens because of the use of selective growth media and a cold enrichment technique. The organism invades epithelial cells and also produces an enterotoxin. The spectrum of illness ranges from simple gastroenteritis to invasive ileitis and colitis that must be distinguished from Crohn disease or ulcerative colitis.

- *Y. Enterocolitica* causes diarrheal illness in adults, including the elderly, and frequently in children, often less than 5 years of age. Children over 5 years of age develop mesenteric adenitis and associated ileitis, which mimic acute appendicitis. Yersinia is less likely to cause

disease in adults. If it does, Yersinia is an acute diarrheal episode followed two to three weeks later by joint symptoms and a rash (erythema nodosum). Treatment is symptomatic. There is no evidence that antibiotics alter the course of the gastrointestinal infection.

- *Clostridium difficile*causes antibiotic-associated colitis and is dicussed later.

o Invasive bacterial gastroenteritis
Certain strains of *E. coli* are invasive, producing an illness indistinguishable from shigellosis. Isolates of *E. coli 0157:H7* have been identified in the stools of patients with a diarrheal illness clinically designated as "hemorrhagic colitis." Infection has been traced to contaminated hamburger meat obtained from a variety of sources, including large international restaurant chains. *E. coli 0157:H7* infection may be complicated by thrombotic thrombocytopenic purpura (TTP), or by the hemolytic uremic syndrome (HUS), which sometimes leads to death. Ingestion of this organism results in severe crampy abdominal pain and fever, followed within 24 hours by bloody diarrhea that lasts five to seven days. Since the organism is shed in the stool for only a short period of time, early stool collections are critical for the diagnosis. Treatment is symptomatic, and antibiotics do not to alter the disease course. In severe cases with possible toxic megacolon, systemic antibiotics may be in order.

Approximately 1,700 serotypes and variants of Salmonella are potential pathogens for humans. A dose of approximately 102–109 organisms is required to produce clinical illness. Salmonella organisms invade the mucosa of the small intestine and particularly the colon. This form of gastroenteritis produces nausea and vomiting followed by abdominal cramps and diarrhea that lasts three to four days and then gradually subsides. In 10% of cases bacteremia of the Salmonella organism occurs, and in approximately 5% there are disseminated infections to bones, joints and meninges.

o *Bacterial gastroenteritis of unknown mechanism*
- *Enterohemorrhagic E. coli*–induced diarrhea tends to occur in neonates and young children. Only occasionally does it affect older children and adults. The pathogenic mechanism of this diarrhea is unclear; adherence of the organism to the intestinal epithelial cell seems to cause intestinal damage. There is no indication for specific treatment except for neonates in a nursery epidemic when oral nonabsorbable aminoglycosides are used.

2.2.4. Traveler's Diarrhea
Traveler's diarrhea is a syndrome characterized by an increase in frequency of unformed bowel movements, typically four to five loose stools per day. Associated symptoms include abdominal cramps, nausea, bloating, urgency, fever and malaise. Traveler's diarrhea usually begins abruptly, during travel or soon after returning home, and is generally self-limiting, lasting three to four days. Ten percent of cases persist longer than one week, approximately 2% longer than one month, and very few beyond three months.

Traveler's diarrhea may be associated with past-infectious irritable bowel syndrome (IBS). *Enterotoxigenic E. coli* (ETEC) is the most common causative agent of traveler's diarrhea. These organisms adhere to the small intestine, where they multiply and produce an enterotoxin that causes fluid secretion and hence diarrhea. Salmonella gastroenteritis, Shigella dysentery, and viral enteric pathogens (rotavirus and Norwalk-like virus) are less common causes of traveler's diarrhea.

Since traveler's diarrhea is usually mild and self-limiting, with complete recovery even in the absence of therapy, therapy should be considered optional (Table 11). The value of prophylaxis for travelers is unclear. Bismuth preparations are helpful, but their use is limited by the large volumes necessary and by their taste. Antibiotic prophylaxis can reduce the likelihood of developing diarrhea, but carries its own risks.

Table 11. Traveler's diarrhea: recommendations for treatment

➢ General
  - o Avoid ice cubes, raw vegetables and fruits, raw fish and shellfish, unrefrigerated food.
  - o Drink canned pop and beer, boiled water.
  - o Drink oral replacement solutions for acute attacks.
  - o Avoid over-the-counter preparations sold locally for acute attacks.

➢ Specific
  - o To provide symptomatic relief of acute attack:
  - o Diphenoxylate 1 tab, 2.5 mg, after each bowel movement to max 8 tab/day
  - o Loperamide 1 cap, 2.0 mg, after each bowel movement to max 8 cap/day
  - o Pepto-Bismol® 30 mL q 30 min ˘ 8 doses
  - o To decrease severity of acute attack:
  - o Co-trimoxazole 1 tab bid po ˘ 3 days
  - o Doxycycline 100 mg bid po ˘ 3 days

➢ Prophylaxis:
  - o Not recommended except for persons who are immunosuppressed or suffer chronic illness. If
  - o indicated, then:
  - o Co-trimoxazole 1 tab bid po ˘ 3 days
  - o Doxycycline 100 mg bid po ˘ 3 days
  - o Ciprofloxacin 500 mg bid po ˘ 7 days
  - o Immunization

o Viral Gastroenteritis
  At least two groups of viruses are capable of producing an acute diarrheal illness.

- *Norwalk Virus*
  The Norwalk virus causes a self-limiting diarrhea and vomiting syndrome that affects children and adults, mainly in winter. Recently, several epidemics have been reported from cruise ship passengers. An incubation period of 24 to 48 hours is followed by a variable combination of fever, anorexia, nausea, vomiting, myalgia, abdominal pain and diarrhea. Spontaneous recovery occurs two to three days later. Immune electron microscopy of fecal filtrates demonstrates the characteristic 27 nm Norwalk virus. No specific treatment is available, except to ensure proper hydration. The vomiting represents delayed gastric emptying; there are no morphologic features of gastritis.

- *Rotaviruses*

Rotaviruses are the most common causes of acute nonbacterial gastroenteritis in infancy and childhood. Rotaviruses invade mucosal epithelial cells, more severe resulting in illness than that caused by the Norwalk virus. Rotavirus infection commonly requires hospital admission and intravenous fluids. Infection occurs mainly in children from 6 to 24 months old, and almost always in winter. Virus excretion is maximum three to four days after the onset of symptoms, and disappears after a further three to four days. The stability of the virus and the large number of viral particles excreted make environmental contamination inevitable, with a high risk of secondary infection in susceptible contacts. For example, 20% of the rotavirus infections diagnosed in pediatric hospitals are nosocomial-acquired in the hospital. Most older children and adults have antibodies to rotaviruses, so any subsequent infection is generally mild.

o   Parasitic Enteritis

The parasites that infect the intestine are divided into three broad groups. These include protozoa, roundworms and flatworms. The flatworms may be further divided into cestodes (tapeworms) and trematodes (flukes). We focus on only a few protozoa seen in immunocompetent Canadian residents.
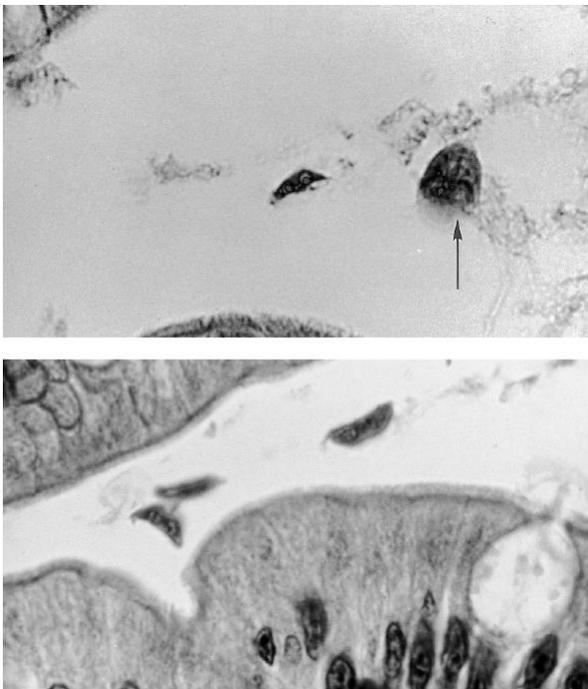
Figure 1A and B. Two high-power views of giardiasis show the typical appearance in cross-section. The crescentic shape and double nuclei are characteristic. One cut shows the organism in longitudinal section (arrow); the organism has the pear shape more familiar from smear preparations. Only one of the two nuclei is visible.

- *Giardia Lamblia*

Giardia lamblia is endemic in many areas of the world, including Canada. Some persons with giardiasis ("beaver fever") present with an abrupt, self-limiting illness that develops one to three weeks after infection, and lasts three to four days. Others may develop chronic and episodic diarrhea associated with bloating and, at times, steatorrhea and a malabsorption syndrome. Diagnosis is made by recovery of the organism. It may be detected in the stool of approximately 50% of patients and in 90% of histologically examined small bowel smear preparations (Figure 1A and B). The treatment of choice in both asymptomatic and symptomatic patients is metronidazole 250 mg t.i.d. for 7 days. Repeat therapy will occasionally be needed to totally eradicate the organism. Quinacrine 100 mg t.i.d. for 7 days also is effective. Some patients develop secondary lactase deficiency with lactose intolerance. This is usually completely reversible after eradication of the organism. Milk and dairy products should be avoided during the treatment phase and for a period of time after treatment so as not to confuse the persistence or recurrence of diarrhea with a persistent infection.

- *Amebiasis*

Amebasis is an acute and chronic disease caused by the organism Entamoeba histolytica. Although there are numerous species of ameba that inhabit the human intestinal tract, E. histolytica is the only variety that is pathogenic for humans. Its manifestations vary from the asymptomatic carrier state, to a severe fulminating illness with mucosal inflammation and ulceration. Asymptomatic carriers harbor cysts in their stools, have no evidence of tissue invasion, but since the cysts are resistant to the outside environment, the disease can be transmitted by these individuals who are unaware of their infective potential. This is in marked contrast to patients with acute or chronic invasive disease, who harbor a trophozoite that cannot survive outside the host.

The acute illness is characterized by diarrhea with the passage of blood and mucus, and by abdominal pain. In its most severe form amebasis may mimic fulminating ulcerative colitis, and may progress to a toxic dilation (toxic megacolon) and perforation of the colon. During the acute illness, trophozoites may be recovered in the stool, from biopsies of shallow ulcers in the rectum, or from smears of rectal mucus. Chronic infectious features may develop many years after the patient has left an endemic area. Patients present with nonspecific bowel complaints and may show radiologic changes in the distal small bowel and colon that mimic ulcerative colitis, cancer or tuberculosis. Diagnosis necessitates recovering trophozoites from the stool. The indirect hemagglutination test can help detect patients with invasive disease.

Systemic dissemination of the ameba may involve other organs, such as the brain, lung, pericardium and liver. Liver abscess is the most common extraintestinal infection by the ameba. Therapeutic agents used for the treatment of amebiasis act at selected sites: intraluminally, intramurally or systemically. Treatment must therefore be individualized to the location of the disease. Asymptomatic carriers are treated with iodoquinol 650 mg t.i.d. for 20 days; this agent acts against amebas located intraluminally. Acute or chronic intestinal disease is treated with metronidazole 750 mg t.i.d. for 10 days. However, because metronidazole is less effective against organisms within the bowel lumen, iodoquinol (650 mg t.i.d. for 20 days) must be added.

- *Cryptosporidia*

Cryptosporidia are a genus of protozoa classified within the subclass Coccidia. In immunocompetent persons, cryptosporidia infection presents as a transient, self-limiting diarrheal illness lasting from one to seven days. Adults are less commonly affected than young children. In most, the illness is mild and medical help is not sought. With immunological incompetence (e.g., HIV/AIDS, neoplasia, hypogammaglobulinemia or concurrent viral infection), a persistent chronic watery diarrhea may occur. Diagnosis is made by demonstrating Cryptosporidia oocysts in the stool or, better still, by mucosal biopsy and examination of the microvillus border for embedded Cryptosporidia oocysts (Figure 2). A successful treatment for Cryptosporidia has not yet been found.
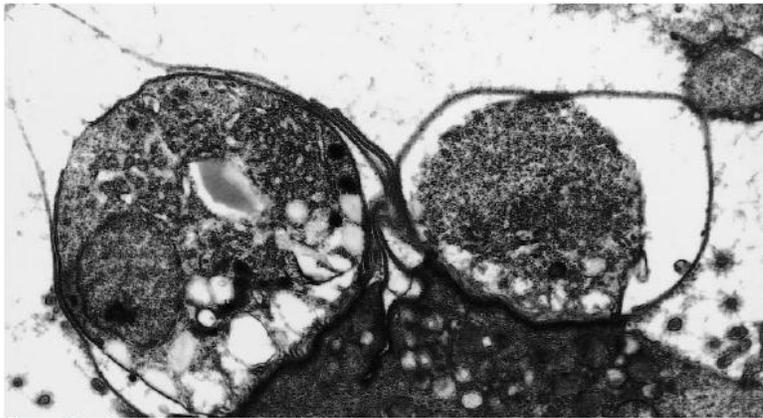
Figure 2. This electron micrograph of cryptosporidiosis in the small bowel shows the characteristics intracellular but extracytoplasmic location of the organisms.

2.3. Drugs and Chemicals

Since almost every drug can cause diarrhea, the first question to ask a patient is "What medications, both prescribed and over-the-counter, are you currently taking?" Discontinuing the drug is often the only therapeutic move required. Although many drugs can cause diarrhea, little is understood about the ways in which they do so. The common causes of drug-induced diarrhea with pathogenic mechanisms follow.

2.3.1. Antibiotics

Antibiotics are the most common cause of drug-induced diarrhea. Diarrhea occurring in asscociation with the use of antibiotics is termed AAD, antibiotic-associated diarrhea. The condition is usually self-limiting. The development of pseudomembranous colitis (PMC) in association with antibiotics may be a serious and sometimes life-threatening condition. The increased incidence of PMC can follow the use of virtually any antibiotic. It may occur months after antibiotic exposure, and may occur without a past history of antibiotic use. The frequency of diarrhea or colitis does not appear to be related to dose or route of administration of the

antibiotic. Symptoms can occur while the patient is on the antibiotic, or within six weeks following its discontinuation.

Only increasing age is clearly identifiable as a risk factor. The diarrhea is usually loose with mucus. Frank bleeding is uncommon. The diarrhea can be devastating, with up to 30 bowel movements in a 24-hour period. The diarrhea may be associated with varying degrees of abdominal pain and low-grade fever. Depending on the severity of the diarrhea and the amount of fluid loss, hypotension, shock and even death have been reported. In many patients the problem is self-limiting and resolves spontaneously with discontinuation of the antibiotic.

PMC is an endoscopic and histological diagnosis. PMC is usually associated with the recent intake of antibiotics and is often associated with the demonstration of toxin in the stools produced by *Clostridium difficile*. Thus, AAD is not necessarily associated with PMC, and PMC is not always associated *C. difficile* infection not be treated but only if the toxin is produced. In recent years, a number of newly recognized and apparently more virulent strains of *C. difficile* have been reported.

An accurate history is usually sufficient to suggest the diagnosis of PMC, and a sigmoidoscopy may be all that is required for confirmation. The presence of copious amounts of mucus and typical raised white pseudomembrane plaques which are not washed away are characteristic features seen on sigmoidoscopy. Colonoscopy is recommended, because the plaques may be seen in the right colon beyond the reach of the sigmoidscope, and the diagnosis would be otherwise missed. Biopsies help confirm the diagnosis (Figure 3A and B). Isolation of *C. difficile* toxin in the stools provides the diagnosis. If it is certain that there is no other likely cause for the diarrhea, treatment can be undertaken while awaiting assay results, although it is usually possible to quickly obtain a sigmoidoscopy to demonstrate the pseudomembranes. If symptoms are resolving with discontinuance of the antibiotic, no further therapy may be indicated. In mild cases, metronidazole 250 mg p.o. t.i.d. for 7–10 days is effective. In severe hospitalized cases the drug of choice is vancomycin 125 mg p.o. q.i.d. for 14 days. Vancomycin is poorly absorbed and central nervous system and renal toxic effects are uncommon. The high cost of this medication limits its use, even though the eradication rate of the *C. difficile* is high. It must be stressed that the vancomycin must be given orally, and not systematically. If oral therapy cannot be used, as with severe ileus or recent surgery, parenteral metronidazole is used. Some 20% of treated patients will have at least one recurrence of symptoms, PMC or *C. difficile*, usually within 4 to 21 days of stopping antibiotic treatment. In this case, another course of metronidazole or vancomycin should be given. If this fails, then pulse doses of vancomycin may be effective. Cholestyramine (Questran®) binds the toxin and can provide symptomatic relief even though it will not eliminate the microorganism. In extreme cases of fulminant non-responsive disease, colectomy, may be necessary.
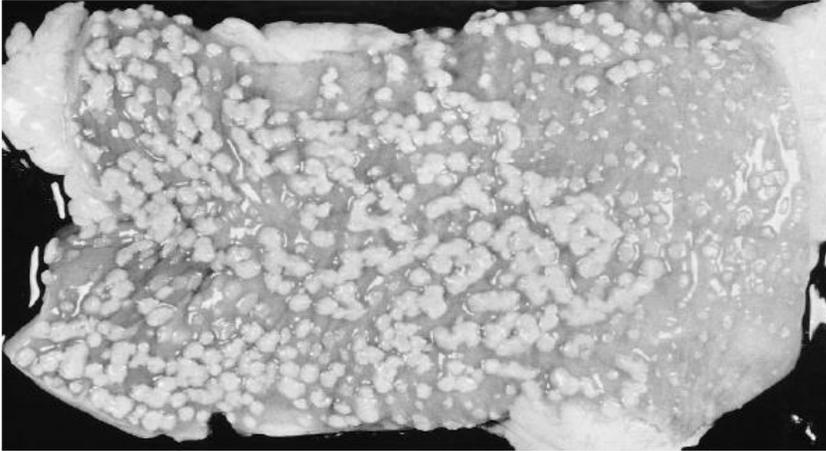
Figure 3A and B. The confluent white patches of pseudomembraneous colitis are typical. In Figure 3B the pseudomembrane is seen to arise like a volcano from a point of mucosal damage and is composed of an exudative fibrin and neutrophils.

2.3.2. Magnesium-Containing Antacids

The osmotically-induced diarrhea produced by Mg2+ is usually mild. A change to a magnesium-free, aluminum-containing antacid is all that is required to control the diarrhea. The use of magnesium-containing antacids is a common cause of diarrhea in dyspeptic patients. Magnesium can be used to induce diarrhea by rare patient with the Münchausen syndrome who seek medical attention for self-induced problems.

2.3.3. Antiarrhythmic Drugs

The antiarrhythmic drugs most commonly associated with diarrhea include quinidine, procainamide and disopyramide. The mechanism involved is unknown. Changing the antiarrhythmic drug usually stops the diarrhea.

2.3.4. Other Medications

Colchicine, often administered for acute gout, produces diarrhea as a common side effect. It resolves with discontinuance of the medication. The mechanism of the diarrhea is unknown, but may relate to an intestinal cytotoxic effect of colchicine. Antimetabolites (e.g., methotrexate) often cause diarrhea as a result of damage to the small or large bowel mucosa. This type of diarrhea can be devastating and difficult to control. Except for rehydration and stopping the drug, little can be done. Diarrhea and cramps occur in at least 5% of persons taking misopostol (an E2 prostaglandin) for gastro protection when concurrently consuming nonsteroidal anti-inflammatory drugs (NSAIDs). Proton pump inhibitors (PPIs) are commonly used to treat dyspepsia. Diarrhea occurs in 1-5% of persons taking a PPI, and may resolve by switching from one PPI to another, or from a PPI to an histamine-2 receptor antagonist. With lansoprazole, but not other PPI medications, well documented cases of microscopic colitis have been reported.

2.4. Chronic Diarrhea
Mechanisms

There are at least four basic mechanisms that cause chronic diarrhea, including osmotic, secretory and exudative factors, and abnormal intestinal transit (Table 12). Often, diarrhea results from more than a single mechanism. If the diarrhea ceases when fasting, then an osmotic cause for the diarrhea is suspected. A significant osmotic gap in the stool water may be present but, under normal clinical circumstances, this is not measured. Examples include diarrhea after ingesting milk (and resulting from lactase deficiency), taking drugs such as magnesium-containing antacids, or the excessive use of artificial sweeteners (eg., chewing gums) such as sorbitol and mannitol, which contain polycyclic alcohols. If the patient's diarrhea persists when fasting (such as may occur at nighttime when the diarrhea awakens the person from sleep), a secretory diarrhea is likely. Secretory diarrhea usually arises from infection or inflammation associated with toxigenic and invasive bacteria. Secretory diarrhea may also result from the spillage of excess bile acids into the colon (choleretic enteropathy) or from the cathartic effect of hydroxy fatty acids arising from the colonic bacterial action on malabsorbed fat (or fermented carbohydrate substrates). Very rarely, secretory diarrhea can arise from a tumor producing an intestinal secretagogue (e.g., pancreatic islet cell tumor producing vasoactive intestinal peptide or gastrin). Exudative diarrhea results from mucosal damage to the small or large bowel, which interferes with absorption of salt and water, and may be associated with the exudation of serum proteins, blood, and mucus and sloughed cells. This mechanism is seen in infectious, inflammatory and neoplastic disorders.

Table 12. Pathophysiologic mechanisms of chronic diarrhea

Major Disturbance	Probable Mechanisms	Examples/Associated Conditions
➢ Osmotic	o Maldigestion	- Antacids, laxatives
		- Pancreatic insufficiency, disaccharidase deficiency
	o Malabsorption	-Carbohydrate malabsorption, congenital chloridorrhea
➢ Disorders of intestinal transit	o Slow transit ("blind loop syndrome") – excessive contact time	-Fistulas, strictures (such as in the patient with Crohn disease), diabetic neuropathy
	o Rapid transit – insufficient contact time	-Intestinal resection, hyperthyroidism, irritable bowel
➢ Secretory	o Bacterial enterotoxins	-*Vibrio cholerae*e, enterotoxigenic *E. coli*
	o Secretagogues	-Bile acids, fatty acids, ethanol, prostaglandins, phenolphthalein, dioctyl sodium sulfosuccinate, VIP, gastrin, calcitonin
➢ Exudative	o Increased passage of body fluids into lumen	-Ulcerative Colitis, Crohn disease

Disorders of intestinal transit may give rise to diarrhea secondary to abnormal intestinal motility in hyperthyroidism or diabetic neuropathy. Scleroderma leads to bacterial overgrowth and steatorrhea (as can the rapid transit in hyperthyroidism). The mechanism of diarrhea in these conditions relates to a combination of bacterial overgrowth, bile salt wastage and disorders of motility (slow or rapid intestinal transit).

2.4.1. Osmotic Diarrhea

Retention of solute molecules within the bowel lumen generates osmotic forces that retard the normal absorption of water and even act to draw water from the circulation into the intestinal lumen (Table 13).

Practical examples and may include poorly absorbed carbohydrates, or poorly absorbed divalent ions (e.g., phosphate, sulfate and magnesium) and are the laxative constituents of several common antacids and saline purges. Since the "pores" through which ions are absorbed are highly charged, these polyvalent ions tend to be absorbed slowly. Thus, they accumulate within the intestinal lumen, raise the osmolality, and diarrhea results.

Some carbohydrates are poorly absorbed by everybody; for example, was developed to be a nonhydrolyzable, nonabsorbable disaccharide that would act as a cathartic. The action of lactulose mimics the effects of *primary lactase deficiency*. This common condition normally develops after weaning in the majority of African-, Caribbean- or Asian-Canadians, and also occurs in about a third of persons with southern European ancestry. The unabsorbed lactose acts osmotically to retain water in the small intestine. In fact, any disease that interferes with carbohydrate absorption (e.g., impaired intraluminal digestion due to pancreatic disease, primary disaccharidase deficiencies, and secondary disaccharidase deficiencies due to small bowel disease) will lead to osmotic diarrhea. Since carbohydrates are not inert in the colon, their metabolism leads to further osmotic forces. Once carbohydrate reaches the fecal flora, anaerobic fermentation occurs. Intermediary products are ethanol as well as formic, succinic and lactic acids. These products are further consumed to varying degrees. CO_2 and H_2 are rapidly absorbed, and in the breath exhaled air. Excess gas production causes borborygmi and flatus rich in H_2. Short-chain fatty acids (SCFAs) are also produced (acetic, propionic and butyric acids), and account for the acidic stool pH noted in diarrhea of carbohydrate malabsorption. In addition, the SCFAs may result in colonic secretion and worsen the diarrhea caused by the presence of osmotically active particles.

Table 13. Causes of osmotic diarrhea

➢ Carbohydrates	o Specific disaccharidase deficiencies
o	o Glucose-galactose malassimilation
	o Mannitol, sorbitol ingestion ("chewing gum diarrhea")
	o Lactulose therapy
➢ Divalent ions	o Magnesium sulfate (Epsom salts)
	o Sodium sulfate
	o Sodium phosphate
	o Sodium citrate
	o Magnesium-containing antacids

The caloric loss due to carbohydrate malabsorption is diminished to the extent that SCFAs are be absorbed from the colon (where they may be used as nutrients by the colonocytes), thus "salvaging" some 75% if the malabsorbed carbohydrate energy that enters the colon. If there are large amounts of malabsorbed carbohydrate entering the colon, and the amount of SCFAs produced exceed the absorptive capacity of the colon, than the osmotically active SCFAs cause diarrhea. The excess SCFAs acidify the stool, less SCFAs are absorbed, and the osmotic diarrhea worsens. Osmotic diarrhea should stop when the patient stops ingesting the poorly absorbed solute.

As the extent of carbohydrate malabsorption increases, more short-chain fatty acids are formed than can be reabsorbed. This results in diarrhea due to the presence of osmotically active short-chain fatty acids. The stool pH consequently begins to fall, which further decreases colonic salvage. In persons with osmotically-induced dirrhea, there will be a detectable positive osmotic gap – that is, stool osmolality minus stool Na^+ plus stool K^+ times 2 (multiplied by 2 to account for anions) is greater than 50, the size of the osmotic gap being approximately equivalent to the concentration of poorly absorbed solutes in fecal water.

2.4.2. Secretory Diarrhea

The small intestine normally secretes as well as absorbs fluid and electrolytes. Normally the secretion rate is lower than the absorption rate, and the net effect is absorption of fluid. For clinical purposes, it is best to consider inhibition of ion absorption and stimulation of ion secretion together (Table 14).

Table 14. **Causes of secretory diarrhea**

➢ Pathophysiologic mechanisms
  o Enterotoxins
  o Circulating secretagogues (VIP, clcitonin, prostaglandins, serotonin)
  o Increased hydrostatic pressure and tissue pressure
  o Gastric hypersecretion (Zollinger-Ellison Syndrome)
  o Pancreatic hypersecretion
  o Laxatives (ricinoleic acid, bisacodyl, phenolphthalein, oxyphenisatin, dioctyl sodium sulfosuccinate, aloe, senna, danthron)
  o Bile Salts
  o Fatty acids

➢ Clinical Syndromes
  o Acute secretory diarrhea
  o Chronic secretory diarrhea
    − Surreptitious laxative ingestion
    − Pancreatic cholera syndrome (VIP)
    − Medullary carcinoma of the thyroid (calcitonin)
    − Ganglioneuroma, ganglioneuroblastoma, neurofibroma
    − Zollinger-Ellison syndrome (gastrin)
    − Malignant carcinoid syndrome (serotonin)
    − Idiopathic secretory diarrhea
    − Congenital chloridorrhea (some cases)
    − Secreting villous adenoma
    − Total villous atrophy of small bowel mucosa
    − Niacin deficiency
    − Intestinal lymphoma
      ▪ Miscellaneous
    − Intestinal Obstruction
      ▪ Intestinal distention/ileus

The first class of bacterial secretagogues comprises large (MW 84,000), heat-labile proteins (LT), of which cholera enterotoxin is the prototype (Table 12). The LT stimulate secretion by activating mucosal adenylate cyclase and thus increasing cAMP levels in the mucosa. The intracellular "messenger" for secretion is less well defined; cyclic AMP is considered important, although there are additional steps that nvolve intracellular levels of $Ca2+$ and the calcium regulatory protein, calmodulin. The second class of secretagogues comprises smaller proteins that are heat-stable (ST). The ST of *E. coli*, stimulates secretion by activating mucosal guanylate cyclase, leading to higher levels of cyclic GMP in the mucosa.

Secretion is also stimulated experimentally by paracrine hormones, luminal factors (e.g., dihydroxy bile acids and fatty acids), neurotransmitters, prostaglandins and physical factors (e.g., distention). Putative secretagogues include vasoactive intestinal peptides (VIP) in the pancreatic cholera syndrome, calcitonin in medullary carcinoma of the thyroid, gastrin in the Zollinger-Ellison syndrome, serotonin in the malignant carcinoid syndrome, and glucagon in glucagonomas. Prostaglandins are also potent stimulators of intestinal secretion. Diarrhea secondary to prostaglandin-stimulated intestinal secretion is a common side effect of orally administered prostaglandin analogues (misoprostil).

The intestinal distention that occurs with obstruction or ileus also produces a local secretory state in the bowel proximal to the obstruction. The mechanism may be related to changes in permeability (as tight junctions are stretched and broken) and perhaps direct neural stimulation of secretory mechanisms. Secretory diarrhea maybe characterized clinically by 1) large volume, stools (often >1 L/day); 2) a stool osmolar gap of < 50 mOsm/L; and 3) diarrhea contains during fasting (between makes and overnight); there is a measured stool osmolar gap of < 50 mOsm/L; and 4) there is no excessive fat, blood or pus in their stools, but often develop depletion in fluid, Na^+ and K^+.

Therapeutically, the offending agent must be removed. A variety of therapies that influence the secretory process (e.g., somatostatin, prostaglandin inhibitors, phenothiazines, calcium channel blockers, α-2-adrenergic agonists and lithium cholestyramine for bile acid – reduced diarrhea) may be effective. ORT is useful for maintenance of hydration, for bile acid-induced diarrhea, cholestyramine works well unless there has been a greater than 100 cm resection of the terminal ileum.

With more extensive resections (>100 cm) there will be both steatorrhea and bile salt wastage, and treatment must be focused on the steatorrhea as long as the loss of electolytes and water doesn't lead to severe depletion, in which case intravenous fluid replacement may be necessary.

2.4.3. Exudative Diarrhea

Structural disruption of the intestinal wall by diffuse ulceration, inflammation, infiltrations and tumors will add cellular debris, mucus, serum proteins and blood to the intestinal lumen. The effects on stool volume will be most pronounced when the lesions also involve the colon, since there will be little opportunity for normal mechanisms of colonic fluid and electrolyte absorption to compensate for the increased volume of luminal contents common examples of exudative diarrhea would include inflammatory bond disease (IBD), and colorectal cancer (CRC).

- Intestinal Transit and Diarrhea

The basal electrical rhythm of the small intestine alters the excitability of the muscle cells. The motility patterns of the small intestine consist of three essential patterns: 1) migrating motor complex (MMC), periodic bursts of contractile activity lasting at least 5 minutes that are succeeded by periods of quiescence and appear to migrate down the small intestine at a slow rate of less than 5 cm/min; 2) minute rhythm, regular groups of between 3 and 10 contractions that occur at intervals of 1 to 2 minutes, separated by periods of quiescence, and appear to migrate down the small intestine at a rapid rate of 60–120 cm/min; and 3) migrating action potential complex, a single ring contraction or single burst of spike potentials that migrates down the intestine at a rate exceeding 90 cm/min. These forms of small intestinal motility control the rate at which material travels along the intestine, and hence arrives at the anus. Gastrointestinal motor activity also determines the time and degree of contact between food, the digestive enzymes, and the absorptive epithelium. Accelerated transit of material through the gut produces diarrhea by limiting the time available for digestion and absorption.

The ileocecal valve is important to gut function. It extends over a 4 cm length of distal small intestine, and produces a high pressure zone of about 20 mm/Hg. Distention of the ileum results in a decrease in the ileocecal sphincter pressure, whereas distention of the colon results in an increased pressure in this area. The ileocecal valve slows down intestinal transit (ileal "break"), and also prevents backwash or regurgitation of contents from the colon. Surgical removal of the ileocecal valve results in rapid intestinal transit as well as the potential for bacterial overgrowth from colonic fecal "backwash." Lastly, premature evacuation of the colon because of an abnormality of its contents or because of intrinsic colonic "irritability" or inflammation results in reduced contact between luminal contents and colonic mucosa, and therefore diarrhea.

2.4.4. Specifc Disease Causing Malabsorption and/or Chronic Diarrhea

The three common causes of chronic diarrhea (Celiac disease, Crohn disease, and Ulcerative colitis, and Irritable bowel syndrome (IBS)) are considered in separate sections.

- Disaccharidase Intolerance

Disaccharide intolerance is a characteristic symptom complex resulting from the ingestion of ordinary dietary quantities of disaccharides, which produces a symptomatic diarrhea. The cause is a deficiency of one or more disaccharidases, but not all people with such a deficiency will experience symptoms, possibly because of a low dietary load, or slow emptying from the stomach. Dietary carbohydrates are presented to the surface of the jejunal mucosa in the form of isomaltose, maltotriose and three major disaccharides – maltose, sucrose and lactose. Trehalose, a disaccharide contained in young mushrooms and in certain insects, is a minor component of modern Western diets.

Deficiencies of disaccharidases may be *primary* (hereditary) or *secondary* (acquired) deficiencies. Characteristically in primary deficiencies, which are rare, only one enzyme is involved; the deficiency is present at birth (with the exception of the common adult-onset form of lactase deficiency), not associated with intestinal disease, and is irreversible because primary lactase deficiency is uncommon in Canadians with northern European ancestors. Secondary deficiencies usually involve all the disaccharidases, may occur at any age, are associated with a disorder of the small intestinal mucosa, and may be reversed if the intestinal disorder (e.g., celiac disease, small intestinal bacterial overgrowth (SIBO) or acute enteritis) resolve.

Table 15. **Anatomic approach to the causes of chronic diarrhea**

➢ Gastric
  o Excessive use of antacids*
  o Hypergastrinemia/Zollinger-Ellison syndrome
  o Postoperative unmasked celiac disease, lactase deficiency or pancreatic
  o insufficiency
  o Postoperative dumping syndrome
    *
➢ Small intestine
  o Celiac disease*
  o Crohn disease*
  o Bacterial, viral or parasitic infection*

- o Whipple's disease
- o Lymphoma
- o Intestinal infiltration: scleroderma, amyloidosis, diabetes

➢ Large bowel
   - o Colon neoplasia*
   - o Irritable bowel syndrome*
   - o Inflammatory bowel disease*: ulcerative colitis, Crohn disease

➢ Drugs
   - o Antacids*
   - o Antibiotics*
   - o Alcohol*
   - o Antimetabolites
   - o Laxatives
   - o Digitalis
   - o Colchicine

➢ Metabolic
   - o Diabetes*
   - o Hyper-and hypothyroidism
   - o Addison's disease
   - o Carcinoid syndrome
   - o VIPoma syndrome

*Common causes

The clinical manifestations of disachharidase deficiency (disaccharide intolerance) result from osmotic diarrhea following ingestion of the disaccharide which cannot be digested into absorbable monosaccharides. The affected individual develops, abdominal distress, bloating, borborygmi flatus and diarrhea. The severity of the diarrhea varies with the disaccharide load, the degree of deficiency of enzyme activity and any associated/ causal intestinal disease. Although often unnecessary, the clinical diagnosis can be confirmed by direct enzyme activity or assay of jejunal mucosal biopsies or by indirect methods for detecting disaccharide malabsorption (e.g., the hydrogen breath test after an oral load of appropriate disaccharide). For children and adolescents (who have high nutritional requirements) and for adults who enjoy milk, low-lactose milk is available. It can also be prepared by adding yeast lactase (available in commercial form, Lactaid®) to milk and refrigerating it for 24 hours.

Delayed-onset (adult-onset) hereditary lactase deficiency is extremely common and probably "normal" for humans. Beginning as early as age two years and as late as adolescence in others, the activity of lactase in the majority of the world's populations drop sharply. This is the result of the genetically controlled "switching off" of lactase synthesis by intestinal cells. Individuals of northern European ancestry normally maintain intestinal lactase activity throughout adulthood, so that if they develop lactase intolerance, an underlying cause such as celiac disease must be identified.

- Short Bowel Syndrome

The severity of symptoms following resections of large segments of the small bowel relates to the extent of the resection, to the specific level of the resected small bowel, whether the colon is still in place, to the reason for which the resection was undertaken. A reduction in the dietary intake of long-chain fats will reduce the severity of diarrhea in >100 cm resection with steatorrhea, whereas a sequestrant of bile acids such as cholestyramine, colestipol or aluminum hydroxide is needed for therapy of the bile acid diarrhea arsing from a resection of <100 cm.

The short bowel syndrome may also be complicated by hyperoxaluria and nephrolithiasis. Normally dietary oxalate is excreted in the feces, bound to calcium as an insoluble complex. In persons with steatorrhea, fatty acids in the intestinal lumen preferentially bind to calcium, leaving the oxalate soluble and available for absorption in the colon. The short bowel syndrome may also give rise to cholelithiasis; with extensive bile acid malabsorption lithogenic bile will be produced, predisposing to gallstone formation.

If less than 100 cm of the distol ileum is resected (for example, for Crohn disease), diarrhea will result from the moderate loss of the active reabsorptive pathway for bile adics, and the spillage of these malabsorbed bile acids into the colon, where a secretory diarrhea results. If greater than 100 cm of the distol ileum is lost, bile acid malabsorbtion will be severe, the ability of the liner to synthesty adequate amounts of bile acids from cholesterol will be exceeded, insufficient bile acids are secreted into the intestinal lumen (less than the critical micellar concentration), and lipids are not solulized and are malabsorbed. The result is steatorrhea.

- Postgastrectomy Maldigestion and Malabsorption

Postgastrectomy malabsorption frequently follows gastric surgery performed for the treatment of massive obesity, complicated ulcer disease, or gastric cancer. The small size of the gastric remnant causes inadequate mixing of food with digestive juices, particularly after a gastroenterostomy. With the loss of the pylorus, there may be rapid gastric emptying ("dumping"), poor mixing of bile and pancreatic secretions (especially if there is a Billroth II partial gastrectomy with a ronx-en-y anastomesis), by passing the site of maximal absorption of iron, calcium, and food-stimulated release of secretion and cholecystokinin (CCK) from mucosal endocrine cells and rapid transit down the small intestine. Incoordinated secretion and poor mixing of bile and pancreatic juice leads to fat maldigestion. Small bowel intestinal overgrowth (in a blind loop or following vagotomy) results in maldigestion of fat, carbohydrate, protein, vitamins and minerals. Gastric surgery that allows food to enter into the upper small intestine without dilution and with minimal digestion may "unmask" clinically occult celiac disease, lactase deficiency or pancreatic insufficiency.

Chapter 8: Celiac Disease

H. J. Freeman, N. Gujral and
A. B. R. Thomson

1. Definition

      Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is a life-long disorder characterized by malabsorption of macronutrients and micronutrients along with mucosal inflammatory changes in the proximal small intestine (duodenum), sometimes extending more distally into the jejunoileum. These appear to be precipitated by ingestion of gluten peptides found in wheat rye and barley. As a result, many celiac patients have intestinal or extra-intestinal symptoms, while others may be entirely asymptomatic. Little is known about the initial events that lead to celiac disease. By definition, however, clinical and histological improvement results from a strict gluten-free diet, and relapse occurs with re-introduction of dietary gluten.

2. History

Clinical GEM

> Celiac Disease occurs in about one percent of the Canadian population. Learn to suspect and test for it in persons with typical gastrointestinal symptoms, as well as knowing when to screen for celiac disease in persons with associated disorders, such as autoimmune conditions.

      Celiac disease may have been described as early as the first century AD. However, the link with gluten was only first established during World War II when it was noticed that some Dutch children improved with wartime food shortages and became worse with re-introduction of cereals. This association soon led to the definition of gluten sensitive enteropathy. Although early autopsy descriptions for celiac disease are available, an evolution in technology for procurement of small intestinal biopsies led to earlier clinical diagnosis, and an explosion of information on many disorders of the small intestine, besides celiac disease. In recent years, the extended recognition of clinical features and protean presentations of celiac disease has resulted in markedly improved awareness. Finally, development of improved screening methods in the laboratory has resulted in appreciation that celiac disease is common, particularly in Europe and North America, with rates of about 1 in every 100 persons.

      Definition of celiac disease in adults depends on two sequential criteria: *first*, demonstration of the typical biopsy changes of untreated celiac disease; and *second*, improvement with absolute dietary gluten restriction. Most often, resolution of diarrhea and evidence of weight gain is sufficient to establish "improvement". In others, especially in children, a second set of intestinal biopsies after a prolonged period of dietary gluten restriction may be needed to document this improvement.

3. Epidemiology

3.1. High Risk Populations

      The true prevalence of celiac disease has not been defined, in part, because many are now recognized for the first time with "atypical", few or no symptoms. Some have suggested that screening measures have especially increased recognition of celiac disease, at least in comparison to those known to have already established disease.

      This has resulted in the conceptual notion of the so-called "celiac iceberg": clinically evident disease may form only a minority of the overall disease burden that is largely sub-clinical and lies "below the surface", often initially diagnosed only later in life (Figure 1).
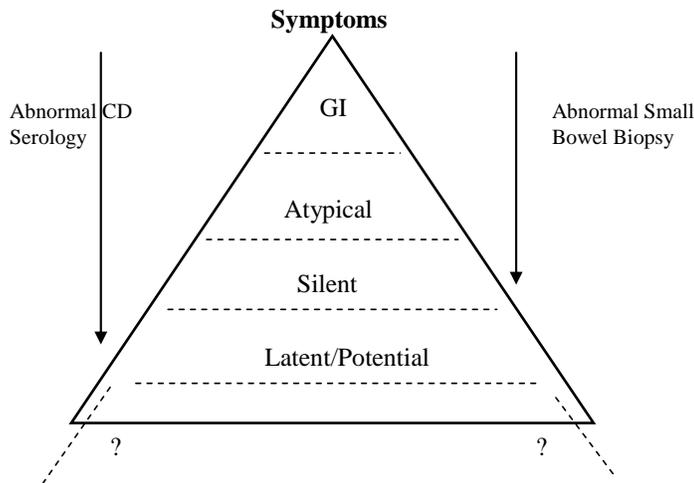
Figure 1. Schematic representation of the celiac iceberg phenomenon.

In North Americans, the reported general population prevalence is approximately 1:100 (1%) with a range of 1:80 to 1:140 (1.25% to 0.71%). A study in Swedish youth (<20 years old) diagnosed with Type 1Diabetes confirmed the low prevalence (0.7%) of diagnosed symptomatic CD at initial onset of clinical diagnosis, but document by screening an increasing prevalence of silent CD during a 5-year follow-up to reached an overall prevalence of 10% (Larsson 2008). Thus, the prevalence of an association with CD in high risk groups may increase over time. High-risk groups that exceed this general population prevalence are listed in Table 1.

Table 1. High Risk Populations for Celiac Disease

- o Relatives, especially first-degree
- o Iron or folate deficiency anemia
- o Osteomalacia or osteopenic bone disease
- o Insulin-dependent diabetes (type1), especially children
- o Liver disease, especially AIH and PBC*
- o Genetic disorders, including Down and Turner's syndrome
- o Autoimmune thyroid disease
- o Skin disorders, particularly dermatitis herpetiformis
- o Reproductive disorders, including unexplained infertility
- o Neurological disorders, including ataxia, epilepsy and MG*
- o Other disorders, including Addison's, IgA nephropathy.

*AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; MG, myasthenia gravis.

The prevalence of CD in dyspeptics is similar to that in the community at large (Giangreco et al. 2008). About 34% of persons with CD are diagnosed in persons over the age of 60 years (Johnson et al. 2008). While they may be present with the usual gastrointestinal symptoms, their presentation may be subtle, and they are more likely to present with iron deficiency, autoimmune thyroiditis, osteoporosis and bone fractures, as well as non-Hodgkin lymphoma (Freeman 2008). Most often, in adults, the disease is diagnosed in females, compared to males. However, for unknown reasons this female sex preponderance disappears with increased aging. In the elderly, the prevalence rates in females and males are similar.

Table 2. Differences between children and adults with CD

	Children	Adults
o Female/male ratio	1.6:1	5.7:1
o Typical symptoms	63%	31%
o Average months to diagnosis	8	90
o Mucosal atrophy	86%	52%

Even within a country the size and population of Sweden, there is considerable variation in the risk of developing CD (Olsson et al. 2009). This raises once again that there might be an environmental factor(s) that trigger the onset of symptoms with a genetic risk of CD and who are exposed to gluten. These may include perinatal infections, or viral infections such as Adenovirus 12 and Hepatitis C virus (Plot and Amital, 2009). Further suggestions for a perinatal virus infection triggering CD come from the observations that "girls with the diagnosis of CD and patients of both sexes with a family history of CD have a different pattern of seasonality of birth from the general population (Lewy et al. 2009).

3.2. Age at Diagnosis

In the past, CD was largely diagnosed in children, who were classically described as having symptoms and signs becoming clinically evident from the ages of 4 to 24 months. The timing was possibly owing to the time of introduction of cereal grains into their diet. At the other end of the age spectrum, there are numerous differences between children and adults with CD (Vivas et al. 2008) (Table 2). Anti-tTG IgA levels were higher in children, and correlated with the degree of villous atrophy.

Now, however, it is appreciated that most clinically evident celiac disease is usually first detected between ages 25 and 40 years, not during childhood. Furthermore, in recent years the initial definition of celiac disease in the elderly has become increasingly appreciated, with some studies recording that about 20% of celiacs are older
than age 60 years.

Clinical Gem

> While the peak age of diagnosis of persons with celiac disease is 25-40 years of age, initial diagnosis of celiac disease may be established at any age, including the elderly.

3.3. Geographic Distribution

The geographical distribution of CD seems to have followed the spread of wheat consumption and the migratory flows of mankind. The highest reported prevalence of celiac disease is from western European countries, North America, particularly Canada and the United States, and Australia. These are all areas where Europeans emigrated. Celiac disease also occurs in the Indian subcontinent, particularly in the Punjab region of northwest India as well as in Indian emigrants to the United Kingdom and Canada. Sprue is probably underdiagnosed in Central and South America. Celiac disease also occurs in the Middle East, Africa, (especially in North Africa), and Asia, although it appears to be very rare in blacks and orientals. Celiac disease has also been described in First Nations persons living on the west coast of Canada; these persons sometimes also have other concomitant immune-mediated disorders.

4. Pathogenesis

Celiac disease results from the interaction between dietary gluten and specific immune, genetic and environmental factors. The current pathogenesis can be summarized as follows: in genetically-primed individuals, an inappropriate T-cell mediated immune response occurs against ingested dietary gluten, the major storage protein of wheat and related grains. This response leads to inflammation mostly in the proximal small intestine, loss or shortening of intestinal villi, and both intestinal as well as extra-intestinal symptoms. When gluten is withdrawn from the diet, these abnormalities improve, or disappear.

4.1. Immune Factors

Gluten generally refers to the entire protein content of wheat, rich in glutamine and proline. Most proteins or peptides that arrive in the proximal small intestine can be digested by luminal and brush border hydrolytic enzymes into amino acids and peptides. Gluten and other proline-rich proteins are poorly digested in the normal human small intestine, because of an apparent deficiency of prolyl-endopeptidases. A number of gluten peptides that may be up to 50 amino acids long can result from this hydrolytic process. For example, undigested gliadin (the alcohol-soluble fraction of gluten) molecules include the 33-mer (composed of 33 amino acids) and 19-mer (composed of 19 amino acids) alpha-gliadin fractions. This is resistant to enzyme digestion, and most of this gliadin remains in the intestinal lumen after gluten is ingested. Gliadin may directly damage the surface epithelium, causing increased IL-15 expression. In addition, gliadin may cause the activation of cytotoxic intra-epithelial lymphocytes that destroy specific epithelial cells with MICA on the surface.

Gliadin peptides may also permeate the epithelial barrier, likely during intestinal infections, or if there is increased permeability (possibly genetically-based, or after surgery), gliadins indirectly cause damage through interaction with lamina propria antigen-presenting cells. Gliadin (high in glutamine) entering the lamina propria may also be deamidated by the enzyme, tissue transglutaminase. This causes conversion of glutamine in these peptides to negatively-charged glutamic acid residues.

The resultant peptides contain sequences that are able to uniquely bind to HLA class II molecules DQ2 or DQ8 on antigen-presenting cells. This permits interaction with the T-cell receptor on gliadin-reactive CD4+ T-cells causing release of tissue-damaging mediators, including proinflammatory cytokines (eg., interferon-gamma). As a result, villous atrophy and crypt hyperplasia develop along with activation and expansion of B-cells which produce antibodies. A humoral or B-cell immune response also appears to be directed towards the

exogenous antigen, gluten (19-mer alpha gliadin fraction), and the autoantigen, tissue transglutaminase.

The toxic peptides, such as the 19-mer, trigger an innate immune response (Maiuri et al. 2003), characterized by the production of IL-15 by epithelial cells and lamina propria dendritic cells (Di Sabatino et al. 2006). There is some evidence that this response is a generalized response in all individuals, but is amplified in CD patients (possibly due to a lower threshold to IL-15) who only get disease as a result of adaptive immune system involvement (D. Bernardo, 2008). IL-15 affects the epithelial barrier, both by increasing the permeability through disruption of the tight junctions (Clemente et al. 2003; Matysiak-Budnik et al. 2003) and acting on intraepithelial lymphocytes (IELs) promoting IFN-γ production as well as a potent cytotoxic activity particularly by NKG2D$^+$ cells (Hue et al. 2004; Meresse et al. 2004). Therefore, immunoadaptive peptides, like the 33-mer, can now reach the lamina propria, where they are presented by dendritic cells to gluten-specific T cells (Nilsen et al. 1995; Rossi et al. 2005).

Regulatory T-cells (Tregs) may show impaired suppressor in CD (Granzotto et al. 2009), raising the possibility that defects in immune tolerance may be part of the pathogenesis of CD. In CD, small intestinal gluten-reactive CD4 (+) T cells bind to the immunodominant gliadin epitopes. The binding to DQ2 is enhanced by the extracellular deamidation of specific glutamine residues by endogenous tissue glutaminases in the lamina propria (Skovbjerg et al. 2008).

TG2 can be both deamidate and transdeamidate peptides, and this propensity is dependent both on substrate affinity and reaction conditions (Stamnaes et al. 2008). The ability of TG2 to hydrolyze the iso-peptide bonds between two peptide substrates represents a novel route for the generation of deamidated T cell epitopes in CD.

tTG2 is on the cell surface, intracellularly, as well as in the extracellular matrix. Anti-tTG antibody inhibits intestinal epithelial cell differentiation and induces proliferation, increases BBM permeability, activates monocytes, and disturbs angiogenesis (Caputo et al. 2009). The authors suggest that these multiple functions suggest that the presence of antibodies to tTG does not simply reflect an epiphenomenon. Other authors have suggested that anti-EMA antibodies are merely bystanders, not related to pathogenic mechanisms (Cianci et al. 2008). After a GFD has been initiated, anti-tTG antibody deposits disappear from the serum after they first disappear from tissue (Caputo et al. 2009).

There are eight Ca2+-dependent transglutaminases that catalyze the cross-linking or deamidation of proteins, thereby playing a role in CD, IBD and cirrhosis. After dietary gluten peptides have been deamidated by the enzyme transglutaminase 2 (TG2), the T-cells are recognized and an inappropriate immune response results. There are large variations in the amount of deamidation between different peptides, and between individual glutamine residues within each peptide (Dørum et al. 2009). The authors suggest that "...the rate of deamidation by TG2 appears to be a factor of importance for the T-cell response to gluten in celiac disease".

A two-dimensional gel proteome reference map using MALDI-TOF ms analysis has been developed (Simula et al. 2009), and will be useful for future research on CD, including "...to identify the variability in protein expression levels, in isoforms expression, or in post-translational modifications associated to pathology or to a therapy".

NMR (nuclear magnetic resonance) has been performed on blood and urine of persons with untreated CD (Bertini et al. 2009). The elevated urine levels of indoxyl sulfate, meta-[hydroxyphenyl]proprionic acid and phenyl acetylglycine suggest that there are alterations in the gut microbiotica. Since these abnormalities returned to normal in 95% of the persons when treated with a gluten-free diet for a year, these alterations were likely the result of the gluten-

associated small intestinal inflammation. In contrast, the reductions in total Bifidobacterium and B. longum population in the feces as well as from duodenal biopsies of both treated and untreated CD patients raises the possibility of this being a pathophysiological abnormality which may have a therapeutic implication (Collado et al. 2008).

A serological response to commensal bacteria occurs in persons with untreated CD (positive seroreactivity to ASCA [anti-Saccharomyces cerevisiae], 49; OmpW [a Bacteroides caccae T-on-B-linked outer membrane protein], 60%; and I2 [Pseudomonas fluorescens-associated sequence], 86%) (Ashorn et al. 2009). Serum levels of ASCA, anti-I2 and anti-OmpW antibodies decreased upon withdrawal of gluten-free diet.

Dendritic cells show increased secretion of IL-6, IL-8 and IL-12 from autologous T cells in response to gliadin in persons with or insilent CD, although the response is higher in CD (Rakhimova et al. 2009). IL-12 induced IFN gamma is the main proinflammatory signal in CD, but IL-17 producing T cells have also been identified (Castellanos-Rubio et al. 2009). Wheat gliadin induces significantly greater production of IL-1 beta, TNF-alpha and IL-23 from PBMC in CD than do non-CD PBMC (Harris et al. 2008). IL-1 beta itself triggers IL-23 secretion and regulated its production. The IL-6 promoter variant -174C increases the risk of developing CD in females (Dema et al. 2009).

IL-15R induces a more intense immunological response in CD than in non-CD persons, and leads to a secondary response of production of nitrites and IFNγ (Bernardo et al. 2008). The higher IL-15Rα and lower IL-15 response threshold lead to a magnified effect and intestinal damage. IL-15 and cytosolic phospholipase A2 are included in the NKG2D-mediated cytolysis of cytotoxic T lymphocytes (Tang et al. 2009). This observation of the importance of NKG2D may help to open the way for new therapies in CD. The production of anti-tTG IgA is directly correlated to the production of anti-DGP (anti-deamidated gliadin peptide) IgA and IgG (Marietta et al. 2009).

These authors speculate that "…in well-established celiac patients, anti-tTG IgA is produced by a set of B celss that are reacting against the complex of tTG-DGP in the absence of tTG-specific T cell" (the hampton-carrier theory).

In children with normal duodenal villous architecture and normal or abnormal serology (latent CD), or with increased gammadelta IELs, 85% and 66% showed subepithelial anti-TG2 intestinal deposits (Tosco et al. 2008). This may prove to be a way to assess the likelihood of a genetically IgA predisposed (based in HLA alleles to develop CD).

In active (untreated) CD, there is lower phosphorylated ERK (extracellular response kinase) and higher JNK (c-Jun amino terminal kinase) in peripheral blood mononuclear cells (Broide et al. 2008). This reflects aberrant regulation of the p21/mitogen-activated proteins (MAP) kinase pathway. After six months of a GFD, these altered values of the ERK and JNK returned towards normal, suggesting that this aberrant kinase response was the result of the active small intestinal inflammation.

The immunogenetics of CD have been renewed, and stress the importance of T cell-mediated immune responses to the pathogenesis of CD, and the use of a genome wide association study which implicated multiple new risk variants, implicating genes involved in the immune system (Dubois and van Heel 2008).

4.2. Genetic Factors

Celiac disease occurs in about 10 to 20% of first-degree relatives of the index patient. HLA genes encoding for HLA-DQ2 and HLA-DQ8 proteins are needed to develop celiac disease. However, their presence may occur in many without celiac disease, since 30% of the Caucasian populations carry HLA-DQ2, but only 1 in 100 will develop CD (Heap and van Heel 2009). While HLA-DQ2 and DQ8 are necessary for the development of CD, certain HLA DQ/DR combinations have a higher relative risk for the development of CD, and the HLA-DQ gene-dose effect influences the strength of the gluten-specific T-cell response (Vermeulen et al. 2009). There are shared as well as distinct HLA alleles in T1DM and CD (Smyth et al. 2008), suggesting that there may be common biological mechanisms in both diseases.

The DQB1*O2 allele influences tTG antibody titers and the clinical and hisological expression of CD (Nenna et al. 2008). The tTG antibody titers are HLA-DQB1*O2 dose dependent, with higher levels in homozygous individuals, and greater clinicopathological expressivity of CD in those with at least one allele.

Genes within the HLA-DQ locus contribute about only 40% of the genetic influence in CD. Using microarray analysis on homogenates from epithelial cells from duodenal biopsies from persons with CD as well as healthy controls, 102 genes were found to have altered expression (Bracken et al. 2008). Validation of significantly altered genes was performed by RT-PCR and immunohistochemistry. This profile of the molecular changes from the epithelial cells in CD provides a focus for the study of novel candidate genes.

In sisters, brothers and parents with CD, high-risk HLA types were found in 57%, 71% and 58%, respectively, but CD was found in only 29%, 15% and 6%, respectively (Megiorni et al. 2009).

There is an association between the interleukin-23 receptor and CD in populations from Finland (Einarsdottir et al. 2009), as there also is such an association for Crohn disease and ulcerative colitis patients in Sweden. The dietary (gluten) and genetic (HLA DQ2 and 8) components of CD may have been in place for years (latent or silent) disease before CD becomes triggered to become symptomatic. Suggested triggers include viral infection, stress, surgery, pregnancy, and childbirth.

During assembly of the HLA class II molecules, they became associated with an invariant chain peptide called CLIP (class-II-associated invariant chain peptide). In CD, there is an alternate CLIP sequence associated with HLA-DQ2 and 8 which has superior binding properties in the peptide binding groove of these HLA molecules (Wiesner et al. 2009). This superior binding arising from the alternate CLIP sequence may contribute to the pathogenesis of CD.

This indicates that these genes are necessary but not sufficient alone to cause the disease. Non-HLA genes may also be important, as genome wide association studies have identified some other genes that may increase risk of celiac disease.

Clinical GEM

HLA-DQ2 and DQ8 are necessary but not sufficient by themselves to cause celiac disease.

4.3. Environmental Factors

A number of environmental factors may play a role in pathogenesis of celiac disease. . Studies have shown that childhood exposure to wheat, barley, and rye in the first 3 months or in month 7 onward significantly increased their risk for developing CD-associated autoantibodies, compared with exposure at 4 to 6 months (Ivarsson 2005; Norris et al. 2005). Breast feeding may be protective and introduction of dietary gluten prior to 3 months of age may increase the risk of disease development. Some viral infections (adenovirus, rotavirus) have also been implicated in earlier studies. Identifying these environmental triggers will be important to explain why some genetically at-work persons who have consumed gluten for many years may first develop symptoms at an older age.

5. Clinical Features

The clinical features of CD are summarized in Table 3, which lists some of the more common and less common clinical features in children and adults. Most clinicians assume that childhood celiac disease and adult celiac disease are similar, but differences, particularly in their pathogenesis and clinical features, do occur. Indeed, some, but not all physicians believe that disease first detected in adults reflects long-standing sub-clinical disease in children that only becomes clinically evident as adults. Others believe that the disease may be much more heterogeneous, and may become initially activated in a genetically-predisposed person much later in life.

Table 3. Common and Less Common Clinical Features of Celiac Disease in Adults and Children

➢ Commo n
- o Children: - diarrhea & failure to thrive
- o Adults: - diarrhea, weight loss & anemia with iron or folate deficiency

➢ Less Common
- o Children: - short stature & delayed puberty
- o Adults: - osteopenia, dental enamel hypoplasia, hypertransaminesia, hyposplenism, polyneuropathy, ataxia, infertility, alopecia

5.1. Childhood Celiac Disease

Most children with celiac disease become clinically apparent after age 4 months, but often before 2 years. Historically, this was believed to be related to the introduction of dietary cereal grains as well as weaning from breast feeding. Diarrhea is commonly recorded, but occasionally, constipation may be present. Most often, in childhood, the disease is insidious with slowing of growth prior to the onset of weight loss. In some, vomiting and severe abdominal distension may occur. With clinically-evident disease, short stature, delay of puberty, pallor and anemia associated with iron and/or folic acid deficiency may develop. Irritability and behavioral disorders, including depression and poor school performance may occur. Rickets was reported in earlier historical experiences, but is not so evident now. Seizure disorder (epilepsy) with cerebral calcifications has been recorded.

The initial detection of celiac disease in older children and adolescents is less common. However, in children on a gluten free diet for previously diagnosed celiac disease, symptoms

may re-develop in this age group, as compliance to a gluten-free diet in older children and adolescents may be less. Some children also have less typical presentations suggesting other disorders including: recurrent and episodic abdominal pain, often with hyperamylasemia (i.e., pancreatitis), and abnormal liver chemistry tests with a hepatocellular injury pattern (i.e., hepatitis). Recurrent aphthous ulcers and dental caries may also be noted.

5.2. Adult celiac disease

There are now recognized to be severe "types" of celiac disease occurring within a spectrum (Table 4). In *classical celiac disease*, diarrhea, weight loss and significant malabsorption of a range of macronutrients and micronutrients may occur. Severe histopathological changes appear in the proximal small bowel mucosa. Changes also develop along the length of the small bowel. Indeed, the extent and severity of these histological changes, the so-called "proximal-to-distal gradient", correlate best with clinical features. With clinically significant malabsorption, for example, histological changes may be severe and extend well beyond the proximal jejunum.

Table 4. Spectrum of Celiac Disease

Types of Celiac Disease (adapted from Setty et al. 2008)

	HLA DQ2/DQ8	Anti-tTG2	Abnormal histology	GI/non-GI symptoms
o Classical	+	+	+	+
o Silent and Occult	+	+	+	-
o Latent	+	+/-	-	-

Further along the small intestine, into the ileum, the morphological changes are less severe and may be patchy in distribution. This may simply reflect exposure in the most proximal small bowel to normally higher concentrations of ingested gluten peptides, since studies have shown that the distal small bowel is in fact very sensitive to gluten peptides if they are infused through long intestinal tubes. With more extensive disease and malabsorption, diarrhea and weight loss occur.

After removal of dietary gluten, clinical improvement occurs with resolution of diarrhea and weight gain. This is usually accompanied by at least partial resolution of abnormal histological changes, first from the most distal portions of the small bowel, and later from more proximal small bowel (i.e., "distal-to-proximal gradient").

Clinical GEM

In addition, to the classical form of celiac disease, in which the patient with intestinal symptoms or with symptoms and signs of malnutrition or nutrient deficiencies, some persons will have clinically silent (occult) celiac disease, and be suspected as having celiac disease because of their having an associated (often autoimmune) condition. Latent celiac disease is a form of sprue in which the person has at one point in time both normal serology and intestinal morphology, but at a later time the intestinal biopsy becomes abnormal.

In some, clinically silent or ***occult celiac disease*** may be present. Few or no intestinal symptoms may be evident. These persons are often suspected from conditions associated with celiac disease (Table 5). In these, only limited histological changes are detected in the most proximal small bowel and only isolated nutrients absorbed primarily at this site may become deficient (eg., iron deficiency anemia). More than enough normal small intestine is present more distally to permit absorption of other nutrients so that diarrhea and weight loss are not seen. Another clinically silent form is ***latent celiac disease***. This was initially reported in persons with dermatitis herpetiformis. In this entity, the small intestine appears to be histologically normal, and serology for celiac disease is initially normal.

Table 5. Intestinal and extraintestinal conditions associated with Celiac Disease

- ➢ Intestinal
    - o Esophagus – squamous cell Ca, adenocarcinoma
    - o Stomach – lymphocytic gastritis; pernicious anemia
        - – celiac disease (classical, occult, latent)
        - – ulcerative ileojejunitis
        - – tropical sprue
        - – collagenous sprue
        - – diffuse small intestinal lymphoma
        - – early aberrant T-cell lymphoma (EATL)
        - – refractory sprue, types 1 and 2
        - – unclassified sprue (sprue-like intestinal disease)
    - o Small Bowel
    - o Colon – microscopic colitis, IBS
    - o Liver – AIH, AIC, PBC, PSC, ideopathic transaminitis
    - o Pancreas – 2° pan-insufficiency, severe insufficiency, diabetes, autoimmune pancreatitis
    - o Nutritional abnormalities - short stature, osteopenic bone disease, iron and vitamin deficiencies, unexplained weight loss

- ➢ Extra-intestinal
    - o Neuropsychiatric and CNS
        - – Chronic fatigue syndrome
        - – Irritability
        - – Depression
        - – Peripheral neuropathy
        - – Epilepsy with intracranial calcifications
        - – Gluten ataxia syndrome (gait and limb ataxia) Paresthesias
        - – Night blindness
        - – Autism
    - o Teeth – dental enamel defects
    - o Lung – fibrosing alveolitis
        - – Bird fancier's lung
    - o Hematopoietic – iron deficiency anemia, hemorrhage
        - – Thrombocytosis
        - – Howell-Jolly bodies

- IgA deficiency
  - o Musculoskeletal – atrophy, tetany, weakness, myalgias
    - autoimmune connective tissue disorders: Sjorgren's syndrome, RA, lupus
    - osteoporosis
  - o Endocrine - secondary hyperparathyroidism, insulin-dependent DM, autoimmune thyroid disease, autoimmune adrenal disease; delayed puberty
  - o Integument - Follicular hyperkeratosis and dermatitis
    - petechiae, ecchymoses
    - edema
    - dermatitis herpetiformis
    - acrodermatitis enterohepatica
  - o Obstetrical - infertility, obstetrical complications (miscarriage), amenorrhea
  - o Renal – IgA nephropathy
  - o Miscellaneous - Downs syndrome, Turners syndrome
    Delayed puberty, slow growth

Abbreviations: AIC, autoimmune cholangitis; AIH, autoimmune hepatitis; CD, celiac disease; DM, diabetes mellitus; IBS, irritable bowel syndrome; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis.

Adapted from: Green PHR, Rostami K, Marsh MN. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg 39.; and Crowe SE. *2007 AGA Institute Postgraduate Course*: page 25.

5.3. Associations

Neurological disorders occur in about 10% of persons with CD. Anti-tTG2 is associated with intestinal disease, whereas anti-tTG 6 IgA and IgG has been reported to be independent of intestinal involvement (Hadjivassiliou et al. 2008). Temporal lobe epilepsy with hippocampal sclerosis has been described in association with CD (Peltola et al. 2009).

The prevalence of CD is about 3-fold increase in those with idiopathic epilepsy (Emami et al. 2008). The cerebellar syndrome and small fiber neuropathy may complicate CD, but often do not respond to a gluten-free diet. In a small group of such individuals, intravenous immunoglobulin was therapeutically effective (Souayah et al. 2008). Other neurological disorders associated with CD include dementia and subacute combined degeneration from associated vitamin B12 deficiency (Freeman 2008).

While osteoporosis (intestinal osteopathy) is more common in persons with CD, there is no need to routinely screen all postmenopausal women for CD (Kavuncu et al. 2009), as, in addition, there does not appear to be an excess risk of CD in adult patients with osteoporosis (Legroux-Gérot et al. 2009). However, children may benefit from bone mineral density screening at the time they are diagnosed with CD, especially in those with low body mass index, or with severe mucosal changes on mucosal biopsy (Jatla et al. 2009).

Autoimmune thyroid disease is associated with CD, with the increased susceptibility of each being possibly related through cytotoxic T-lymphocyte-associated protein 4 (CTLA4) (Tolone et al. 2009).

While it is widely recognized that T1DM and CD may occur together, especially in children, the CD is often clinically silent, and even the person's height, body weight, and

haemoglobin concentration may be normal (Jatla et al. 2009). A high index of suspicion and appropriate screening for CD in T1DM is necessary.

It is not clear if the observation that anti-tTG from pregnant CD mothers directly binds to the syncytiotrophoblasts on the surface of the placenta, inhibiting the placental activity of tTG (Anjum et al. 2009), compromising placental function and lead to a poor outcome of the pregnancy. It remains controversial if all pregnant mothers should be screened for CD (Pope and Sheiner 2009).

Oxalate renal calculi are more prevalent in CD, and this is not due to the CD-associated diarrhea or malabsorption, but rather to unexplained hyperoxaluria (Ciacci et al. 2008). Placing the CD oxalate excretors on a GFD returned the hyperoxaluria to normal.

The prevalence of CD in children with Down syndrome is 5.2%, 10-times higher than the general Dutch population (Wouters et al. 2009).

The anemia which occurs in 34% of persons recently diagnosed with CD may be from deficiencies of iron and vitamins, as well as from the inflammation-associated increase in IFNγ, reduction in serum levels of erythropoietin, and thereby anemia of chronic disease (Bergamaschi et al. 2008).

There is a higher than expected rate of eating disorders, (especially bulimia nervosa) in CD, and non-compliance with a GFD is higher in this group (Karwautz et al. 2008).

For children with clinical manifestations suggestive of CD, BMI SDS (Body Mass Index Standard Deviation Score) is more sensitive than height or weight to be used as an indicator of the need to screen for CD (van Dommelen et al. 2008). In children with CD, there is an increased frequency of enamel defects, particularly in deciduous teeth (Ortega Paez et al. 2008). In children with T1DM, 11% were positive for CD-specific antibodies, and 15% had positive thyroid antibodies (Fröhlich-Reiterer et al. 2008). Some persons with CD are hyposplenic, and this may contribute to the increased rate ratio (1.61) of pneumococcal inflation in England in celiac patients (Thomas et al. 2008). CD is associated with thyroid disease. In Sweden, the hazard ratio is 4.4 for hypothyroidism, 3.6 for thyroiditis and 2.4 for hyperthyroidism (Elfström et al. 2008). CD is also occurs in IgA-deficient persons, so are must be aware that the presence of the relatively common IgA deficiency will cause false negative IgA CD serological tests (Cianci et al. 2008).

CD is associated with hyperhomocysteinemia, which is itself associated with an increased risk of cardiovascular disease (particularly stroke), recurrent miscarriage and osteoporatic fractures. The elevated levels of homocysteine in CD normalize on a GFD (Dickey et al. 2008). Supplementation of CD patients who were already on a GFD had an improvement in their psychological well-being, and especially anxiety and depression, when given a daily supplement of B vitamins (Hallert et al. 2009).

Over half of 54 untreated CD children (mean age of 7 years) had reduced serum calcium and vitamin D3 concentrations plus elevated PTN levels, with the hyperparathyroidism returning to normal when a GFD was introduced (Zanchi et al. 2008).

Untreated persons with CD may have an inadequate response to hepatitis B immunization: as compared with CD treated with a GFD where the response rate was 96%, those not on a GFD have an immunization response of only 51%, and the poor response correlated with the degree of nonadherence to the GFD (Nemes et al. 2008).

Dermatitis herpetiformis (DH) is associated with CD. Patients with DH suffer from a papulovesicular eruption which contains IgA deposits in the dermal papillae. The epidermal tranglutaminase, TG3, is distinct from the TG produced by the small intestine, TG2. Patients

with DH and adults with CD have elevated serum levels of antibodies to TG3, as well as to TG2 (Hull et al. 2008).

<div style="text-align:center">Clinical GEM</div>

> Definition of celiac disease in adults depends on two sequential criteria: *first*, demonstration of the compatible biopsy changes of untreated celiac disease; and *second*, improvement with absolute dietary gluten restriction. But the definition is challenging, with the recognition of non HLA genotypes, and biopsy-negative latent/potential disease, and the fact that many patients have few or no typical GI symptoms

Approximately 3% of CD patients will have primary biliary cirrhosis, primary sclerosing cholangitis, or autoimmune hepatitis. These do not respond to a GFD. In contrast, about half of CD patients will have transaminitis associated with a nonspecific hepatitis, both of which normalize on a GFD (Volta, 2009). Rarely, cryptogenic chronic hepatitis or cirrhosis will be found histologically, and this may partially respond to a GFD.

5.4. Refractory Celiac Disease

In some persons with well-defined and treated celiac disease, diarrhea or malabsorption may recur and appear to be refractory to continued dietary gluten withdrawal. Often, these recurrent clinical features are associated with the return of severe histological changes which are typically seen in untreated celiac disease. In most, poor compliance with a strict gluten-free diet is evident as the cause of the recurrence of symptoms and histological signs. Sometimes, the actual source of gluten is ubiquitous, such as pill capsules or communion wafers.

Other causes of refractory symptoms may need to be considered. A second cause of symptoms (i.e., diarrhea and weight loss) may be present, such as an infectious diarrhea. Also, histologic changes in the small bowel due to other related causes (eg., folate deficiency, zinc deficiency) may occur. In these, treatment of the specific infection or the deficient nutrient may be sufficient for the patient to improve.

In others, a concomitant cause for malabsorption may be present. For example, pancreatic exocrine insufficiency with pancreatic calcification may occur, particularly in celiac patients with long-standing malnutrition. On occasion, re-evaluation of the original diagnosis is needed to ensure that a different diagnosis was not initially missed. Finally, diarrhea may be due to a disorder associated with celiac disease, (eg., lymphocytic or collagenous colitis), or a serious complication (eg., lymphoma). An unusual and rare disorder, collagenous sprue, sometimes may occur in celiac disease. In most persons with collagenous sprue severe panmalabsorption with diarrhea, weight loss and marked nutritional and electrolyte disturbance may develop.

In a small number of persons with refractory celiac disease, no specific cause can be identified. Some have a rare syndrome with small bowel histologic changes of variable severity, splenic hypofunction and cavitation of mesenteric lymph nodes. Some eventually develop or have a concomitant intestinal lymphoma.

CD subjects have high levels of TCR gammadelta+ IELs in the small intestinal mucosa, but these elevated levels fall in about half of refractory CD (RCD) type II patients who develop enteropathy-associated T-cell lymphoma (EATL) (Verbeek et al. 2008), with these being a negative correlation between the number of TCR gammadelta+ IELs and aberrant IELs. Intracellular CD3 epsilon is present in IELs and lymphoma cells in CD, but the cell surface lacks the T-cell receptor (TCR) – CD3 complex due to either impaired synthesis or defective association of the TCR chains (Tjon et al. 2008). This results in the premalignant transformation in RCD II.

There is a positive pathogenetic relationship between CD and lymphocytic gastritis (presence of ≥ 25 lymphocytes per 100 epithelial cells) (Prasad et al. 2008). In contrast, while there is a 80% prevalence of antroduodeno-jejunal fasting and fed motility abnormalities observed in untreated CD, which decline on a gluten-free diet (GFD) (Bassotti et al. 2008). Their occasional persistence on a GFD raises the possibility that these motor abnormalities may explain persistent symptoms in same persons with CD who are on a GFD.

Lymphocytic duodenitis is not part of the histological spectrum of CD (Vande Voort et al. 2009). Intestinal T-cell lymphoma are tumors which differ in their association with "enteropathy, intraepithelial or nonepithelial origin, primary or secondary inducement, and T-cell or natural killer-like T-cell immunophenotypic" (Muram-Zborovski et al. 2009). It is suggested that "...a large monoclonal antibody panel [be used] for the differential diagnosis of this heterogenous group of T-cell lymphoma".

Enteropathy-associated T-cell lymphomas (EATL) are T-cell non-Hodgkin lymphomas of the small bowel occurring in persons with CD. The incidence in the Netherlands is 1/105 inhabitants per year, is usually in the jejunum, more often in males, peak incidence in the 7th decade, with the diagnosis usually made by surgical resection (Verbeek et al. 2008).

5.5. Unclassified Sprue or Sprue-like Intestinal Disease

Occasionally, some adults may have diarrhea and weight loss. Severe intestinal mucosal biopsy changes are present, similar to those in untreated celiac disease, but these fail to respond to a gluten-free diet. This may represent a heterogenous group, with no specific cause identified. Some could have a "clinically-resistant" form of celiac disease, whereas others may eventually prove to have a "difficult-to-diagnose" lymphoma. Most remain severely symptomatic with malabsorption and profound wasting despite a gluten-free diet. In some, an abnormal subset of intra-epithelial lymphocytes may be detected with morphologically normal, but phenotypically abnormal lymphocytes (based on immunochemical staining). Most of these persons unfortunately die with uncontrolled malabsorption despite steroid therapy and parenteral nutrition. This suggests that immunohistochemical changes represent a marker of poor prognosis.

6. Malignant Complications

Some of the malignant complications are listed in Table 6. The overall cancer risk in celiac disease is approximately double the rate in the general population. The two main malignancies in persons with celiac disease include adenocarcinoma or lymphoma of the small intestine. Some reports suggest that other sites in the gastrointestinal tract may have an increased rate of malignancy. In particular, hypopharyngeal cancer may occur, possibly in association with iron deficiency anemia. The risk of colon cancer is not thought to be increased.

Table 6. Complications of Celiac Disease

- o Enteropathy-associated T-cell lymphoma (and B-cell lymphoma)
- o Carcinoma of hypopharynx
- o Carcinoma of esophagus
- o Carcinoma of small intestine
- o Refractory sprue
- o Collagenous sprue

Clinical   GEM

In the celiac patient who was previously well on a gluten-free diet, and who then has a recurrence of GI symptoms, assess for possible dietary non-compliance, intestinal lymphoma or adenocarcinoma, development of collagenous sprue or microscopic colitis, intercurrent infections.

Small intestinal adenocarcinoma is an unusual malignancy, but, this cancer is markedly increased in adult celiac disease. These are usually located in the jejuno-ileum, although localization in the duodenum may occur. Like adenocarcinoma that occurs in the colon, an adenoma-to-carcinoma sequence has been proposed. Most often, however, adenocarcinoma occurring in the patient with celiac disease presents late in the clinical course, sometimes with symptoms of a small bowel obstruction. Rarely, this malignancy is the presenting feature of celiac disease. Surgical resection of the carcinoma has the greatest potential for cure, although adenomas and carcinomas may be multifocal and occur elsewhere in the small intestine, thereby presenting a surgical care.

Small bowel lymphoma may also occur in persons with celiac disease. Most are T-cell in type, the so-called enteropathy-associated T-cell lymphoma. However, B-cell lymphomas also may occur. These also occur in the jejuno-ileum, but duodenal lymphoma may also be seem. Most often, these lymphomas present as ulcerating or obstructing tumors. Although splenic atrophy is usually seen in adults, the development of splenomegaly may be a clinical clue to the development of an occult lymphoma. Rarely, the lymphoma may also develop in an extra-intestinal site or may be multifocal.

Involvement of lungs or pleura, and thyroid with T-cell lymphoma in celiac disease has been described, possibly reflecting their common embryonic origins from the intestinal tract. Hepatosplenic T-cell lymphoma, an exceedingly rare entity, has also been reported in celiac disease without evidence of small bowel involvement with lymphoma.

Often, surgical treatment is required for complications, particularly intestinal obstruction. Radiation and chemotherapy have also been used. A lymphoma may be the first presentation of underlying celiac disease. Finally, there is some evidence, primarily from long-term studies in the United Kingdom, suggesting that the continued use of a gluten-free diet may be protective for the development of lymphoma in the person with celiac disease.

7. Diagnosis

7.1. Serology and urine testing

 There are a number of clinical indicators for CD (Table 7). A number of serological tests have been developed that may be helpful for screening for celiac disease. If celiac disease is suspected, a serologically-positive test may confirm suspicion of celiac disease, but a biopsy should be done to determine if changes of untreated celiac disease are present prior to initiating a gluten-free diet.

 Most commonly used serological tests for celiac disease are IgA antibodies to endomysium (EMA) and tissue transglutaminase (tTG). The former is semi-quantitative whereas the latter is quantitative and may be automated. While both serological tests are highly sensitive, false-positive assays may occur in the absence of celiac disease (Table 8).

Table 7. Clinical indications for serological testing for CD

➢ Autoimmune endocrine disorders
  o Insulin-dependent diabetes mellitus
  o Autoimmune thyroid disease
  o Autoimmune adrenal disease

➢ Autoimmune connective tissue disorders
  o Sjogren's syndrome
  o Rheumatoid arthritis
  o Systemic lupus erythematosis

➢ Hepatobiliary conditions
  o Primary sclerosing cholangitis
  o Primary biliary cirrhosis
  o Autoimmune cholangitis
  o Elevated transaminases

➢ Other gastrointestinal disorders
  o Lymphocytic gastritis

➢ Microscopic colitisMiscellaneous conditions
  o IgA deficiency
  o IgA nephropathy
  o Down's syndrome
  o Turner's syndrome

Printed with permission: Crowe SE. *2007 AGA Institute Postgraduate Course*: page 25.

Table 8. Performance Characteristics of Tests for Celiac Disease

	Sensitivity (%)	Specificity (%)
o Lactulose/mannitol ratio in urine	85	46
o Saccharose in urine	60	53
o AGA – IgA	15	100
o AGA – IgG	20	100
o EMA	50	78
o TGA – IgA	77	100
o TGA – IgA and EMA	98	100

Abbreviation: AGA, anti-gliadin antibody; EMA, endomyceal antibody; anti-tissue transglutaminase

The tests may also be positive if there is co-existent chronic liver disease. In addition, the tests are not as helpful if selective IgA deficiency is present, as is the case in about 5% of the general population. This is why it is often recommended to perform a quantitative test for IgA when performing the IgA-anti tTg test.
The anti tTg test is about 95% sensitive and specific to diagnose CD, with false positives or false negatives (Table 9).

Table 9. Clinical indications which are associated with false positive or false negative, serologic testing for CD

➢ False negative
- o True false negative
- o IgA deficiency
- o Children < 2 years
- o Recent gluten free diet
- o TPN
- o Recent steroids, immunosuppressives, anti-TNFs
- o Hematopoietic stem cell transplantation

➢ False positive
- o Congestive heart failure
- o Autoimmune diseases (may be associated with CD which is in a latent phase)
- o Liver diseases
- o Inflammatory bowel disease
- o Silent (potential), potential (latent) celiac disease

Adapted from: Green PHR, Rostami K, Marsh MN. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg 391.

Standardized measurement of transglutaminase antibodies is necessary, because of the very wide range of laboratory sensitivities (69% to 93%) and specificities (96% to 100%) of this

important assay (Li et al. 2009). A standardized method of analysis is also needed to determine quantitatively to gluten content of food and to be certain that "gluten-free" truly represents an accepted low level of gluten (Thompson and Mendez 2008). An electrochemical sensor has been developed to detect gluten in foods, and it performs well compared to the ELISA (Nassef et al. 2008).

In children, IgA antibody testing to tissue transglutaminase (tTG) had the best operating characteristics, with a sensitivity of 93%, specificity of 98%, PPV of 98% and NPV of 92% (Basso et al. 2009). In children with IgA deficiency, AGA IgG II testing was positive. In children over 2 years and without IgA deficiency, tTG IgA and AGA IgG II were equivalent in performance. These serum parkers fell towards normal within a year of a gluten-free diet.

Whole blood tests have been developed for the diagnosis of CD, and while the sensitivity is a little lower (91%) than the standard serum-based ELISA tests, their specificity is comparable (98%) (Raivio et al. 2008).

A cost-effective, paint-of-care electrochemical immunosensing method has been developed for the detection of serum antibodies to tTG (Pividori et al. 2009), and may provide a means for population screening in a primary care setting.

In children, the tTG may be less reliable than in adults, with a sensitivity of 93% and specificity of 90% (Leach et al. 2008).

Screening for CD using serology may need to be performed several times over an extended time interval. For example, it is accepted that T1DM is associated with CD. The cumulative frequency of positive CD serology in children and adolescents with T1DM rises from approximately 4% to 10% over a 5 year interval (Larsson et al. 2008).

Intestinal permeability tests from urine samples can screen for a wide range of small intestinal diseases, including CD and enteric infections. Monosaccharides (mannitol) and disaccharides (lactulose, saccharose) molecules have been used to investigate intestinal permeability. The use of hyperosmolar lactulose and mannitol test solutions is found to increase the sensitivity of the test in detecting CD. Intestinal permeability is characteristically elevated in untreated CD, with a sensitivity of up to 85% (Table 8). The reason being for this is an increase in the absorption of lactulose (through the paracellular route) due to "leakiness" of the intestine and a reduction in the absorption of mannitol (through the transcellular route) due to a reduction in surface area as a result of villous atrophy

7.2. HLA Genotyping

Genotyping methods for HLA risk factors are laborious, complicated and costly. An approach which "…exploits linkage disequilibrium between single nucleotide polymorphism (SNDs) and the CD-associated HLA risk factors DQ2, 5 and8…" shares that only six SNPs are needed to predict the risk types carried by greater than 95% of CD patients, with a sensitivity greater than 99%, a specificity of 99.6%, and a predictive value of 94.8% (Monsuur et al. 2008). This method would appear to be excellent for population screening for CD.

Negative testing for HLA-DQ2 and DQ8 could eliminate the need to perform serological tests in persons thought to be otherwise at risk of developing CD, and it is possible that this approach could prove to be cost-effective (Chang and Green 2009). CD-associated HLA allele typing would provide a high negative predictive value to exclude CD in high-risk groups (Donat et al. 2009).

Population screening for CD is not yet advocated, but certainly in high risk groups and possibly on an index basis, a novel HLA genotype method using six HLA-tagging single

nucleotide polymorphisms suitable for high-throughput approaches gives sensitivities and specificities of 95% to 100% in European persons (Koskinen et al. 2009), and may prove to be cost-effective and lead to widening of the indications for screening.

7.3. Endoscopy and Diagnostic Imaging

There are a number of endoscopic features which are thought to be associated with CD. About two-thirds of CD patients will have a mosaic pattern, nodular mucosa, scalloping of folds, and reduction/loss of folds. If there were more than one of these endoscopic markers present, 84% of these persons had CD. The positive predictive value (PPV) was about two-thirds overall for these endoscopic findings (Piazzi et al. 2008).

Endoscopic changes in the upper small intestine by EGD (esophagogastroduodenoscopy) may also be seen with video capsule endoscopy (CE). While the mucosa changes in CD are often in the proximal intestine and are readily within the reach of EGD, CE does not allow detection of subtle endoscopic changes further along the intestine. CE showed a 78% concordance with histology to diagnose CD in those who had failed to respond to a GFD (Maiden et al. 2009). Patchy involvement is unusual, and the typical features (villous atrophy, scalloping, fissuring, mosaic pattern) gradually decreased along the length of the small intestine (Ersoy et al. 2008).

MDCT enteroclysis may prove to be useful to raise the possible diagnosis and its complications of CD (Soyer et al. 2008).

Extending the use of endoscopy to raise the suspicion of CD, optical band imaging enhances the contrast of the mucosal surface without the use of dyes, and provides excellent sensitivity, specificity, PPV and NPV in the evaluation of the villous patterns and optimizing the diagnostic accuracy in celiac disease (Cammarota et al. 2008).

7.4. Histology

Clinical GEM

> At present, the "gold standard" for the diagnosis of celiac disease remains the small intestinal mucosal biopsy

Although the diagnosis of CD can be suspected on clinical or laboratory grounds, or as a result of serological tests, histology of the small intestinal mucosa is still the diagnostic gold standard and must always be performed. Histopathological analysis of small intestinal biopsy samples of individuals with CD is characterized by typical architectural abnormalities. Marsh (Marsh, 1992) has pioneered the theory of a sequence of progression of the CD lesion in the small intestinal mucosa.

The characteristic histopathological findings for untreated celiac disease include crypt hyperplasia and villous atrophy causing a "flattened" mucosal appearance (Figures 2 to 5). Intraepithelial lymphocytosis also occurs, and the lamina propria region shows increased cellularity largely from plasma cells and lymphocytes. Some experts have termed this biopsy appearance as: crypt hyperplastic villous atrophy (*severe* "flat" lesion, Marsh 3 lesion). Over time, the clinical and histological changes revert to normal on a strict gluten-free diet. Most newly diagnosed sprue patients will notice clinical improvement within a few weeks. Histological evidence of improved architecture in the most proximal small intestine may take many months, even years, especially in adults.

Less severe histopathological changes may occur in adult celiac disease and the changes may be patchy rather than diffuse. In children, CD-related histological changes are always present in the duodenal bulb, and sometimes this is the only site to be histologically abnormal (Bonamico et al. 2008). These authors suggest that for the diagnosis of CD, 2 biopsies be taken from the duodenal bulb and 2 from the distal duodenum.

Minimal intestinal lesions are at the very mild end of the spectrum of histological changes in CD. In a three year follow-up study of 209 persons performed in Italy, when CD serology was initially negative and duodenal biopsy showed a minimal lesion, three years later, only one person was on a GFD because of gluten-sensitive symptoms, and was DQ2 and 8 positive (Biagi et al. 2008). This strongly suggests that a minimal lesion plus initially negative endomysial antibodies is unlikely to be CD.

In Sweden, IBD occurred in 0.3% of small intestinal mucosal biopsies showing villous atrophy (VA) (Ludvigsson et al. 2009). Thus, comorbidity other than CD in the biopsy showing VA is rare, and the specificity of CD is high in villous atrophy. The same type of validation needs to be performed in other geographical regions.
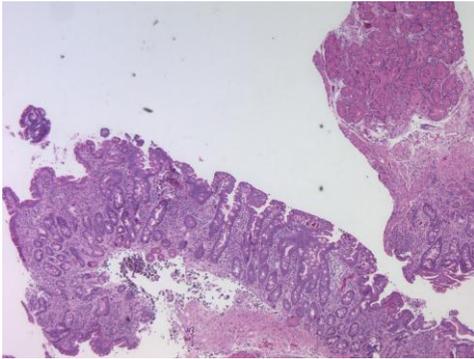
Figure 2
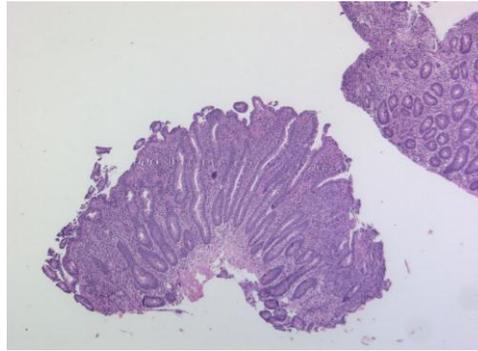
Figure 3
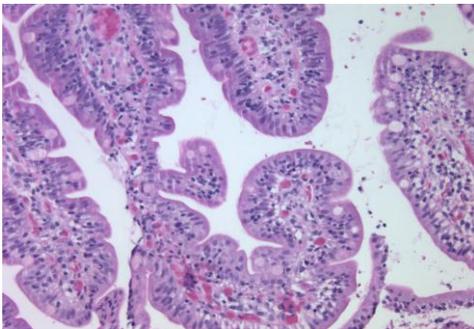
Figure 4
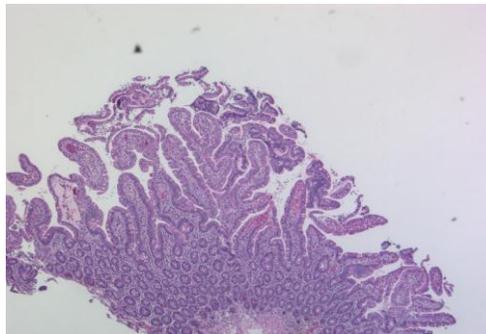
Figure 5

There are many small bower disorders which may mimic CD (Table 10) (Figure 6).
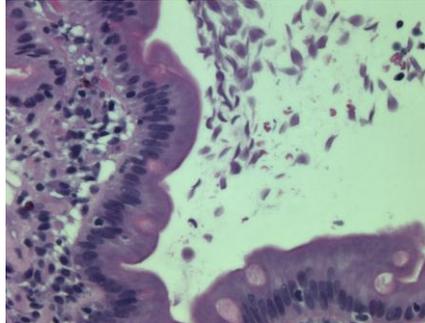
Figure 6

Table 10. Differential diagnoses of a "sprue-like" small bowel biopsy in a patient suspected of having CD

➢ Celiac disease and its variants

➢ Infection
  o post viral gastroenteritis
  o giardiasis
  o small intestinal bacterial overgrowth (stasis syndrome)
  o HIV (immunodeficiency syndromes)
  o MAC (Mycobacterium-avium complex infection)
  o cryptococcus, giardia lamblia, strongyloides
  o topical sprue (infections agent suspected)
  o Whipple's disease
  o Crohn disease
  o Amyloidosis
  o Mastocytosis
  o Histoplasmosis
  o Eosinophilic enteritis
  o Waldenstroms macroglobulinemia

➢ Infiltration
  o Benign
  o Malignant immunoproliferative small intestinal disease (IPSID, ie alpha chain disease), lymphoma

➢ Immune
  o graft-versus-host disease
  o hypogammaglobulinemia

➢ Food
  o food protein hypersensitivity (rye, barley, egg, fish, rice, poultry, cow's milk, soy, other proteins)
  o oats-induced villous atrophy
  o folate, cobalamin, zinc deficiency
  o protein-calorie malnutrition

> Drugs, radiation
>> o NSAIDs, colchicines, neomycin, chemotherapy
>> o Radiation

> Miscellaneous
>> o Zollinger-Ellison syndrome
>> o mesenteric lymph node cavitation syndrome
>> o α-β-Lipoproteinemia
>> o lymphangiectasia
>> o microvillus inclusion disease (children)
>> o Waldenstroms macroglobulinemia

Abbreviations: CD, celiac disease; IPSID, immunoproliferative small intestinal disease

Adapted from: Freeman HJ. *Canadian Journal of Gastroenterology* 2008;22(3): pg 277.

The combination of the presence or absence of villus shortening with or without increased intraepithelial lymphocytes (IELs) may be a helpful distinguishing factor (Table 11).

Table 11. Conditions other than CD, where there may be an increased density of small intestinal intraepithelial lymphocytes (IELs)

No villous shortening, ↑ IELs	Villous shortening, ↑ IELs	Villous Shortening, Normal IELs
o Celiac disease	o Celiac disease	o Tuberculosis (including atypical)
o Tropical sprue	o Tropical sprue	o HIV/AIDS
o Autoimmune diseases/ conditions	o Collagenous sprue	o Common variable inmmunodeficiency syndrome
o Nonsteroidal anti-inflammatory drugs	o Protein intoleranc (cow's or soya milk)	o Whipple's disease
o Crohn's colitis	o Post-infectious diarrhea	o Radiation enteritis
o Microscopic colitis		o Immunoproliferative small intestinal disease
o Bacterial overgrowth syndrome		o Crohn disease
		o Eosinophilic gastroenteritis
		o Autoimmune enteropathy
		o TPN

Abbreviations: CD, celiac disease; IELs, intestinal intraepithelial lymphocytes; TPN, total parental nutrition

Printed with permission: Collins P, Wahab PJ, Murray JA. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg 344; and Daum S, Cellier C, Mulder CJJM. *Best Practice & Research Clinical Gastroenterology* 2005;19(3):pg. 415.

When there is not villus shortening and only an increase in IELs, subtle considerations may be helpful (Table 12).

Table 12. Factors which support the diagnosis of CD in patients with an increased density of intraepithelial lymphocytes (IELs) but no villous shortening

o Family history of celiac disease	o 15% of first-degree relatives are affected
o Concomitant autoimmune conditions	
o Increased density of γδ + IELs	o Risk of celiac disease approximately 5-fold
o Increased density of villous tip IELs	
o HLA DQ2 or DQ8	o Sensitivity 0.84, specificity 0.91
o Gluten dependence	o Sensitivity 0.84, specificity 0.95
	o High sensitivity, low specificity high. Negative predictive value
	o Should be ascertained by gluten challenge or gluten-free diet

Printed with permission: Collins P, Wahab PJ, Murray JA. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg 347.

In some instances special stains may give a clue to the diagnosis of the small bowel condition (Table 13).

Table 13. Histological features which may be used to distinguish the conditions from celiac disease

Cause of malabsorption	Cause of malabsorption
o Collagenous sprue	o Collagenous band below atrophic epithelium
o Mycobacterium-avium complex	o Acid-fast bacilli, foam cells, PAS positive macrophages
o Infection (MAC)	o Congo red-stained deposits with apple-green birefringence in polarized light
o Amyloidosis	
o Crohn disease	o Epitheloid granulomas and characteristic focal inflammation
o Eosinophilic gastroenteritis	o Eosinophilic infiltration
o Lymphangiectasia	o Ectatic lymph vessels
o Lymphoma	o Clonal expansion of lymphocytes
o Mastocytosis	o Diffuse infiltration with mast cells
o Infection	o Parasites may be seen on histologi examination (eg. guardia lamblia, strongyloides), TB, HIV
o Whipples	o Acid-fast bacilli, foam cells, PAS positive, diastase resistant staining in macrophages
	o α_1 antitrypsin deficiency
	o Whipples disease (diastase resistant)
	o MAC (Mycobacterium-avium complex infection)

Abbreviation: MAC, mycobacterium-avium complex infection

Adapted from*:* Freeman HJ. *Canadian Journal of Gastroenterology*2008; 22(3): page 277.

In the patient with diarrhea and or flat malabsorption a novel small bowel biopsy will help to exclude several conditions (Table 13).

Table 13. Conditions causing malabsorption that are usually excluded by a normal small bowel biopsy

➢ Sprue (actually, not always – patchy, treated, immunosuppression, potential – ATG positive, but small bowel biopsy normal)

➢ Hypogammaglobulinemia

➢ α-β-Lipoproteinemia

➢ Whipples (except in very rare circumstances with CNS Whipples)

A *mild* lesion may occur with no significant alteration in villus structure but with increased intra-epithelial lymphocytes. A *moderate* lesion (partial villus atrophy) with less severe change in villus architecture may also occur. Often, these less severe changes are associated with other diseases, rather than celiac disease. However, if detected, further studies should be done to exclude other causes (eg., giardiasis).

A number of small bowel disorders may cause histological changes that appear like untreated celiac disease, but do not respond to a gluten-free diet. Some of these are listed in Table 13. Only the biopsy changes of untreated celiac disease respond to a gluten-free diet.

Table 14. Causes of Severe Biopsy Lesions often confused with Celiac Disease

➢ Sprue Syndromes
  o Celiac disease (classic, occult, latent forms)
  o Refractory sprue (refractory celiac disease)
  o Collagenous sprue
  o Mesenteric lymph node cavitation syndrome
  o Other protein injury (soy protein, milk, other)
  o Unclassified sprue or sprue-like intestinal disease

➢ Infectious Causes
  o Infectious gastroenteritis (childhood)
  o Infections (protozoans, parasites, viral, fungal, mycobacterial)
  o Tropical sprue
  o Stasis syndrome (contaminated small bowe syndrome)
  o Whipple's disease

➢ Deficiency Syndromes
  o Nutrient deficiency syndromes (zinc, vitamin B12, folate)
  o Kwashiorkor
  o Immunodeficiency syndromes (common variable, AIDS)
  o Intestinal lymphangiectasia

➢ Others
  o Crohn disease
  o Graft-versus-host disease
  o Immunoproliferative diseases (lymphoma)
  o Zollinger-Ellison syndrome
  o Autoimmune enteropathy (?)
  o Drugs (sulindac, busulfan, methotrexate)

8. Treatment

> The essential element of management is strict and lifelong removal of gluten from the diet

8.1. Gluten Free Diet

The essential element of management is strict and lifelong removal of gluten from the diet. Gluten is found in wheat, rye and barley. Oats may be tolerated by some patients, theoretically permitting consumption of an increased variety of different foods.

Unfortunately, commercially available oats products are often contaminated with gluten-containing grains during growing, transportation and milling processes. Grains that appear to be safe include rice, buckwheat, corn, millet and sorghum.

Minerals and vitamins should be measured and replaced, if deficient. However, since most celiac patients that respond to a gluten-free diet absorption will improve so that these minerals and vitamins usually normalize without the need for specific supplements. Screening and monitoring for osteopenic bone disease with a bone mineral density test (DEXA scan) is recommended. Growth and development in children also requires monitoring after a gluten-free diet has been initiated. A skilled dietitian is helpful to review the diet initially and to serve as an information source. Patient support groups and online information and other literature may be available, such as, to locate sources of gluten-free products. These gluten free products maybe costly and in some developing countries, they may also be difficult to access.

Treatment compliance is important as a gluten-free diet is protective against the development of lymphoma. Treatment of symptomatic disease may improve nutritional parameters, including bone mineral density measurements. Treatment may eventually result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional as well as biochemical status, including iron absorption parameters.

The patient and their family must be educated in the disease, and accept the need to be on a gluten free diet for life. Any associated nutrient deficiencies must be corrected. Many patients benefit from belonging to the Canadian Celiac Society (http://www.celiac.ca/).

Persons with gastrointestinal symptoms may choose to place themselves on a gluten-free diet, prior to proper investigation and establishment of the diagnosis. This practice must be strongly discouraged, since the PPV for clinical improvement after gluten withdrawal is only 36%, and only 28% PPV for clinical exacerbation after gluten reintroduction (Campanella et al. 2008).

Patients with CD on a GFD who have persistent symptoms tend to have more persisting histological abnormalities than those CD/GFD patients without symptoms, a higher intraepithelial lymphocyte count, and the symptoms that do persist are often different and may be

unrelated to those at the time of diagnosis such as symptoms of gastroesophageal reflux disease, abdominal pain or constipation (Carroccio et al. 2008).

Assessing Quality of Life (using the Short Form-36 health survey, the Gastrointestinal Symptoms Rating Scale, and the Beck Depression Inventory) before and after a GFD demonstrated that within three months, there was a clinically and statistically significant improvement in classical and atypical but not in asymptomatic CD patients (Nachman et al. 2009).

A high throughput, immune-based assay using monoclonal antibodies specific for immunotoxic peptides has facilitated their detection in food (Morón et al. 2008). This may eventually prove to be useful for the establishment of gluten-free foods, as well as providing a means to monitor the action of TG2 on gluten peptides.

8.2. Follow-up

While it may be common to repeat duodenal mucosal biopsies in children after a suitable parent on a GFD, this is generally not recommended in adults, particularly if symptomatic improvement results with resolution of diarrhea and weight gain. In some, with no or few symptoms, and no or minimal changes in blood tests, another biopsy may be needed to show a GFD response (Vécsei et al. 2009).

8.3. Unproven Experimental Therapies

The only treatment currently available for CD is the life-long withdrawal of gluten from the diet. This gluten-free diet (GFD) is expensive, the GFD is not always palatable, and may contribute to the reduced quality of life reported by some persons with CD. Noncompliance with a GFD is often reported in adolescents with CD. Based on the young person's degree of adherence to a GFD (compliers, occasional noncompliers and noncompliers), different strategies may be used (Olsson et al. 2008). It should be noted though that histological changes improve initially in the more distal small bowel, so repeated biopsies from proximal duodenum may show little initial improvement (Jadrosin et al. 2008).

The IFNγ released form gluten-activated T cells enhances intestinal permeability, enhancing even further the transepithelial flux of gluten peptide in T84 cultured epithelial cell monolayers (Bethune et al. 2009). This raises the intriguing possibility of using anti-IFN γ therapy to break this "vicious cycle".

The proposed new Codex Alimentarius Standard for naturally gluten-free foods is a maximum of 20 ppm. Surface-associated proteins on wheat starch may be removed, leaving a product which is sufficiently low in gluten (7 ppm) to be used by persons with CD (Kasarda et al. 2008).

Prolyl endopeptidases (PEPs) may be given to cleave the immunotoxicgluten peptides from cereal proteins (wheat, rye, barley) (Ehren et al. 2008). Using a combination of sequence and structure-based approaches with machine learning algorithms may provide the protein engineering means to develop new food products for use by CD persons.

AT-1001 is the antagonist for zonulin, which is an endogenous signaling protein that transiently and reversibly opens the tight junctions between the cells of epithelial and endothelial tissues such as the intestinal mucosa, blood brain barrier and pulmonary epithelia. The release of zonlin may restore the increased intestinal permeability which results from or may even contribute to the development of CD (Baldassarre et al. 2008). The use of AT-1001 will inhibit zonulin will prevent the opening of the tight junction, blocking s the paracellular route of gliadin absorption.R-spondin 1 is a recombinant, secreted protein which may also have a therapeutic role in CD.

Analysis of gliadin T-cell epitopes has been developed from durum wheat to down-regulate the abnormal T-cell immune response in CD (Silano et al. 2008). These antagonist peptides may prove to represent a useful therapeutic strategy in CD.

Strains of sourdough lactic acid bacteria (Lactobacillus sanfranciscensis LS40 and LS41, and Lactobacillus platarum CF1) have been used to reduce gluten in bread down to 20 ppm, qualifying this as being "gluten-free", as well as enhancing the free amino acid concentration, thereby providing enhanced nutritional properties (Di Cagno et al. 2008).

8.4. Non-Dietary Treatments

The topic of novel non-dietary therapeutic strategies for CD has been removed (Sanz 2009). Gliadin may be neutralized by complexing it with a polymeric binder, and thereby preventing the toxic effects of gliadin on the intestine (Pinier et al. 2009).

Wheats may be genetically engineered to avoid the CD – immunogenic domains, such as by pre-screening for differentiated expression from the homologous alpha-gliadin genes at various genomic loci (Salentijn et al. 2009).

Selected enterococci and Rhizopus oryzae proteases may be used effectively to hydrolyse wheat proteins responsible for CD (M'hir et al. 2009). Combinations of bacterial and fungal proteases when fermented with gluten may decrease gluten concentration by more than 98%.

A reliable extraction protocol has been developed to remove immune responsive gluten proteins in wheat, rye and barley (van den Broeck et al. 2009), which may prove to be useful in the development of foods free of gluten yet still containing non-toxic cereal proteins.

Chapter 9: Crohn Disease

A. B. R. Thomson, Q. Li, M.T. Clandinin, and H. J. Freeman

1. Definition

Crohn disease (CD) may be defined in a number of ways. Simply, "CD is a chronic [life-long], transmural [patchy] inflammatory disorder that may involve any part of the gastrointestinal tract from mouth to anus, mostly found in the ileum, the c[a]ecum and the colon. Characteristic symptoms of this idiopathic inflammatory bowel disease (IBD) are chronic or nocturnal diarrh[o]ea, abdominal pain, weight loss, fever and rectal bleeding" (Shao et al., 2009). It is likely caused by a multifactorial complex interplay among genetic, environmental, microbial, and immune factors in a genetically predisposed host (Mizoguchi and Mizoguchi 2008; Podolsky 2002), with uncontrolled inflammation affecting the mucosa as well as other layers of small intestine and/or colon (Fretland et al. 1990).

There may be a mild or a disabling clinical course with unpredictable relapses, perianal and extraintestinal complications, as well as frequent medical encounters including hospitalization, unpleasant therapies, and surgery. These all contribute to the sufferer's sense of hopelessness, depression, anxiety, sexual disturbances, unemployment, disability or need for sick leave from this debilitating disease (Caprilli et al. 2008).

While Crohn disease (CD) involves primarily the small intestine and more specifically the ileum, ulcerative colitis (UC) is a disease localized to the colon alone (2). Crohn's can affect any area of the gastrointestinal (GI) tract, from the mouth to anus, CD and UC are two separate conditions with distinguishing clinical, endoscopic, and pathological findings, but they do have some overlapping features and may even represent several different diseases with similar characteristics (Hanauer 2006).

Useful Practice Points:

What does the Primary Care Physician (PCP) Need to/Want to Know about IBD?
- o Typical patient presentation & profile
- o Major differential
- o PCP-based investigations
- o First line therapy for new IBD
- o Identify and treat a recurrence

---

2. Demography

Modern management has improved IBD patient survival (Loftus et al., 2007). Because the mortality rate in CD is only slightly higher than in the healthy population, the prevalence of CD has been increasing over time. In most parts of the world, the incidence and prevalence of CD are higher than those for UC. In Canada, the incidence of UC and CD are approximately 5 and $10/10^5$, respectively, and the prevalence is at least 100 to $200/10^5$ (Panes et al., 2007; Loftus 2004; Vind et al., 2006).

Inflammatory bowel disease (IBD) affects approximately 1.5 million people in the United States and more than 2 million in Europe (Ruthruff 2007). In Canada, it has been estimated that nearly 200,000 Canadian men and women suffer from IBD. In the last generation, the incidence of CD has been increasing throughout most of the world (Economou 2008), although in some countries, the rates are beginning to stabilize (Baumgart 2007). The incidence of CD is highest in North America and Europe. The peak incidence is 16-25 years of age (Vind 2006). In adults, there are slightly more women than men with CD (Jacobsen 2006; Loftus 2002), with the reverse seen in pediatric ages (Hait 2005, Panes 2007). Other differences between CD in children versus adults are given in Table 1.

Useful Learning Points

o CD is slightly more frequent in women than men
o 10-15% of CD patients are diagnosed before adulthood
o the peak incidence of CD is 16-25 years, with no secondary peak
o Differences between pediatric-onset vs adult-onset CD
o Disease onset may be influenced by different genetic loci
o Different inflammatory mediators may influence disease course
o Proximal and extensive disease is more common in pediatric-onset disease

Table 1. Differences in the child versus the adult with CD

o Age of diagnosis – more severe clinical course in those who are diagnosed at a young age (see below).
o Site
  – ileum: higher probability of activity
  – Ileocolonic: earlier need for surgery and repeat surgery
o Slightly higher rate in males than females
o More proximal and more extensive disease
o More sever clinical course
o Different genetic loci influence disease onset
o Different inflammatory mediators (Panes et al.2007)

Useful Practice Points:
Why does the Primary Care Physician (PCP) Need to Know About IBD?
o Number of patients   300/105
o Number of PCPs   1/103
o Every PCP will have 2 to 3 IBD patients
o Number of PCP/GI in Canada   35,000 vs 500

CD is more common in Jewish than in non-Jewish persons, and in Caucasians more than African Americans (Ruthruff 2007). Familial distributions of IBD involved first-degree relatives (parent, child or siblings) more often than second-degree or third degree relatives (aunts, uncles, nieces and nephews). Among first-degree relatives, siblings (most often, female siblings) are most often affected with Crohn disease, compared to parents or children (Freeman, 2002). This is in accord with polygenic inheritance (Kirsner 2001). CD has a higher incidence among smokers than nonsmokers (Ruthruff 2007). Cigarette smoking is detrimental in CD: it leads to an earlier age at diagnosis, and a higher likelihood of requiring immunomodulator therapy or surgery. Individuals who smoke and have a diagnosis of CD are at higher risk of a complicated clinical course and increased frequency of exacerbations. Conversely, smoking leads to a later diagnosis of UC, with a better overall clinical course.

3. Pathogenesis

While pathogenesis of Crohn disease is unknown, a current popular working model is that CD is the result of 1) either an exaggerated host immune response, an inappropriate chronic activation of the innate and adaptive mucosal immune systems in a genetically susceptible host (Bouma and Strober 2003) against the intestinal mucosal surface microbiotics, through either the activation of T cells and initial overexpression of inflammatory type 1 helper T-cell(Th1) cytokines (such as tumor necrosis factor-alpha [TNF-α], interleukin [IL] -1, -2, -12, -18, and interferon gamma) (Podolsky, 2002; Ardizzone et al.2005), or 2) a defect in down-regulating the immune response, leading to chronic inflammation in a genetically predisposed person (Shao et al.2009; Shanahan et al.). Various environmental and host factors (e.g. genetic-, epithelial-, immune and non-immune) play a major role in the pathogenesis of IBD (Lakatos et al. 2006). The role of abnormally increased intestinal mucosal permeability in CD is not clear, but will be discussed later.

➤ **Familial and Genetic Considerations**

CD has a familial inheritance pattern that does not follow simple Mendelian models. A positive family history is found in 5–20% of patients with CD and first degree family members of IBD patients are at a 10- to 15-fold increased risk to develop IBD themselves (either CD or UC), somewhat more in CD than in UC (Noomen et al. 2009).

The transmission of IBD from parent to child is low; with one parent with IBD; transmission risk is 7%. If both parents have IBD, there is a 37% risk of transmission (Yang H, et al. *Gut* 1993:517-24). The risk of transmission is higher in members of the Jewish faith (Table 2).

Table 2.

	CD	**UC**
Jewish	7.8%	4.5%
Non-Jewish	5.2%	1.6%

The most convincing evidence for genetic predisposition comes from twin studies, which show increased concordance rates for both UC and CD in monozygotic twins, as compared to non-identical twins. The concordance for CD in monozygotic twins is 35% compared with 7% in dizygotics, with the equivalent in UC being 11 versus 3% (Noomen 2009). The markedly increased concordance rates in identical twins can only be explained by an underlying genetic component.

With the completion of the human genome sequence, it became possible to perform 'genome-wide association studies', providing systematic assessment of the contribution of common variation to disease pathogenesis. This approach has had an unprecedented impact on our knowledge of the genetics of many autoimmune diseases. These studies have resulted in the identification of many novel loci for CD as well as UC, have highlighted the importance of the innate immune system, and have implicated new pathogenic pathways such as autophagy (Noomen 2009).

IBD has been classified as a complex disease complex diseases resulting from the interaction of multiple genetic and non-genetic factors (Goyette et al. 2007). The role of host

genetic regulation of the innate immune response in the pathogenesis of CD has been brought to sharp focus by the identification of the NOD2 (CARD15) mutations (Lakatos 2006).

The NOD2 gene on chromosome 16 q (IBD1) was the first susceptibility gene identified for CD (Hugot 2001; Ogura 2001b) (Table 3). The product of this gene is expressed in many cells, including monocytes, dendritic cells, Paneth cells and intestinal epithelial cells. NOD2 contains an apoptosis-related CARD domain. Further understanding of regulatory elements within non-coding genomic regions and gene–gene interactions will lead to a better understanding of the underlying mechanisms that cause disease (Xavier 2007).

Table 3. The NOD2 gene

o   3 independent mutations of the nucleotide-binding oligomerisation domain2 (NOD2) gene
o   NOD2 gene encodes the NOD2/easpase recruitment domain (CARD) protein
o   CARD15 protein increases susceptibility to CD in Caucasians (18,19)
o   NOD2/CARD15 activate the NF-kB signalling pathway to stimulate the secretion of a defensins (cryptins) (21)
o   There is a gene-dosage effect of NOD2/CARD15 variations (24): the risk of developing CD is 2.4 (95% C12-2.9) for a simple heterozygote, vessus 17.1 (95% CI 10.7-27.2) for persons with two mutant chromosomes, simple homozygotes, or compound heterozygotes

NOD proteins (NOD 1 and 2) recognise peptidoglycan (PGN), a component of bacterial cell walls derived from Gram positive bacteria (Strober 2006), and are expressed predominantly by antigen-presenting cells and epithelial cells (Inohara 2003). PGN is also broken down in endosomes, and is thus a source of MDP (muramyl dipeptide), a substance that is sensed by and activates NOD2. Such activation initiates a mechanism of inhibition of PGN-mediated NF-κB activation and thus causes downmodulation of TLR-induced cytokine production (Strober 2007). Polymorphisms in NOD1 and 2 (also known as CARD4 and CARD15), result in a susceptibility to develop IBD, particularly Crohn disease in the case of NOD2 (Geier 2007). Homozygous mutation in NOD2/CARD15 has been shown to account for 10–15% of patients with CD, and this mutation leads to a decrease in NFκB activation upon stimulation.

There are three independent mutations of the nucleotide-binding oligomerisation domain 2 (NOD2) gene, which encode the NOD2/caspase recruitment domain (CARD) 15 protein, and increase CD susceptibility, but curiously only in Caucasians (Aberu 2005, Cho 2003, Ogura, 2001, Aldhous 2003). NOD2/CARD is involved in the recognition of bacterial peptidoglycan-derived muramyl dipeptides. The NOD2 gene codes for the NOD2 protein, which is a pattern recognition receptor that senses intestinal luminal bacterial breakdown products of peptidoglycans muramyl dipeptide (MDP) (Braus 2009).These activate the nuclear factor-kB (NF-kB) signalling pathway, and stimulate secretion of the antimicrobial α-defensins (cryptins) (Rosetiel 2006).In CD persons who are simple heterozygotes with one mutant chromosome in NOD2/CARD 15, the relative risk for their developing CD is 2.4 (95% CI 2-2.9). In contrast, persons who are simple homozygotes or compound heterozygotes with two mutant chromosomes have a relative risk of developing CD of 17.1 (95% CI 10.7, 27.2) (Economou 2004).

Interestingly, NOD 2 / CARD 15 variants are linked to CD phenotype: ileal disease, strictures (of ileum), and non-perianal fistulas (Brant et al.2003). NOD2/CARD15 mutations may be associated with younger age of diagnosis, ileal or fibrostenotic disease (Ahmad 2002,

Economou 2004); and higher intestinal permeability to sugars in relatives of CD patients (Sachar 2005). There are numerous other CD susceptibility genes. The OCTN genes (organic cation transporters) are linked to perianal CD (Vermeire 2005). The IBD 5 locus (IBD5 region on chromosome 5q 31-33) is linked to susceptibly to develop CD (Rioux 2001). The IL23R gene on chromosome 1p31 encodes A-subunit of the IL-23 receptor (Duerr 2006), and is associated with the development of CD. Other less well-studied CD susceptibility genes include DLG5, NOD1, TLR-4 and -9 (Vermeire 2005).

> **Environmental Associations**

There are numerous environmental associations with CD which may either initiate or continue the inflammatory response (Table 4).

Table 4. Environmental Associations of CD

- o Higher economics development of country
- o Higher personal socioeconomic status (30)
- o Smoking cigarettes (31, 39)
- o Use of NSAIDs
- o Use of Antibiotics
- o C. Difficile infection
- o Upper respiratory tract and enteric infections
- o Psychological Stress
- o Pollution, diet

Adapted from Ardizzone and Bianchi Porro 2005

> **Immune Function**

The innate immune system is the first line of defense against resident luminal microflora and invading pathogens, and can respond to a wide variety of microorganisms. The innate immune system has evolved to monitor the resident microflora and relay danger signals in response to infection by invasive organisms. This response is mediated through the recognition by specific pathogen recognition receptors (PRR) of microbial components, known as pathogen-associated molecular patterns (PAMPs). The PRRs include the members of the Toll-like receptor (TLR) family, which are predominantly cell surface receptors, and the cytosolic Caterpillar-(CARD)/NOD intracellular receptors (Werts 2006). The binding of PAMP ligands to specific PRRs leads to the activation of several intracellular signaling pathways, which include the nuclear factor-kB (NF-kB) and mitogen-activated protein kinase (MAPK) pathways for TLRs and predominantly the NFκB pathway for CARD/NOD receptors.

These pathways in turn lead to the activation of transcriptional programs resulting in the broad-spectrum non-specific killing mechanisms of innate immunity. These mechanisms include synthesis of reactive oxygen species, activation of the complement protein system, secretion of chemokine and cytokines for chemotaxis of phagocytotic macrophages, and secretion of antimicrobial proteins by Paneth cells (Goyette 2007). Paneth cells are specialized epithelial cells located at the base of small intestinal crypts, which monitor the intestinal lumen and are considered important mediators of mucosal innate immune defense. They contribute to host defense and maintenance of the gastrointestinal barrier through the luminal secretion of a number

of antibacterial peptides (defensins, lysozyme and secretory phospholipase A2), which protect nearby intestinal stem cells and control microbial density.

The intestinal lamina propria contains a complex population of immune cells that balance the requirement for immune tolerance to the normal luminal microbiota, but also with the need to defend against pathogens, the excessive entry of luminal microbiota, or both (Abraham 2009). The hallmark of active inflammatory bowel disease is a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells), as well as adaptive immune cells (B cells and T cells). Increased numbers and activation of these cells in the intestinal mucosa elevate local levels of tumor necrosis factor α(TNF-α), interleukin-1β, interferon-γ, and cytokines of the interleukin-23–Th17 pathway (Abraham 2009, Izcue 2008). There is dysregulation of intestinal CD4+ T cells: In CD, for example, there is increased production in the intestinal mucosa of the Th17 cytokine interleukin-17 and the Th1 cytokines interferon-γ and TNF-α. Interleukin-23, secreted by macrophages and dendritic cells, may contribute to Th17 proliferation, survival, or both (McGeachy and Cua 2008). Levels of interleukin-23 and Th17 cytokines are elevated in the colonic mucosa in both Crohn disease and ulcerative colitis (Abraham 2009).

Studies of IBD in mice and humans implicate dysregulation of intestinal CD4+ T-cell subgroups in their pathogenesis. The defective T-cell mediated regulation is associated with a disruptive interaction between the immune system and gut luminal factors. Animal studies have identified a CD4+ CD25+ cell population which expresses the FOXP3 transcription factor (Hori 2003). This regulatory T cell population (Tregs) is thought to suppress the activation of effector T cells at the level of the antigen-presenting cell, and produce IL10 and transforming growth factor (TGF) β. In addition to this 'naturally occurring' Tregs, there are also 'adaptive' Tregs, the so-called Tr1 and Th3 cells (Huibregtse 2007). Regulatory T cells appear to be key players of immune regulation, and they have important functions in suppressing unwanted inflammatory responses towards self-antigens, and the antigens of endogenous intestinal bacteria.

The role of B cells in IBD has not been as extensively studied as that of T cells. Intestinal B cells produce IgA antibodies, which contribute to immune protection without provoking inflammation. In animal models of colitis, both anti-inflammatory and proinflammatory roles of B cells have been described.

The proposed mechanism for the development of IBD involves the deregulation of the adaptive immune system stemming from an imbalance between regulatory and effector-cell immune responses to luminal antigens or other antigen (e.g. self-antigens). In contrast to innate immunity, adaptive immunity generates a slow and more targeted response involving antigen-specific recognition and immune memory. The GALT represents the largest part of the body's immune system, and given the large surface area of the mucosal epithelium, the immune system encounters more antigens in the gut than any other location in the body. In addition, since most of the antigens encountered by the mucosal immune system are derived from food proteins and commensal bacteria, the immune system must remain relatively unresponsive to avoid responses to harmless antigens and maintain epithelial integrity. It has been proposed that tolerance to these luminal antigens, also known as oral tolerance, occurs through a state of active cellular suppression or clonal anergy of immune reactive cells induced by specialized regulatory T cells (Mowat 2004). The proposed role of adaptive immunity in IBD is derived from genetic studies indicating a central role of the MHC in the development of IBD and also from in vivo observations in IBD patients of abnormal patterns of cytokine production and immune cell

responses (excessive Th1 response in CD and Th2 response in UC), of modulations in regulatory T and B cell functions, and of antibodies to luminal antigens (Mizoguchi 2006).

➢ **Intestinal Permeability**

The integrity of the epithelium is maintained mostly through a combination of intercellular adhesion structures and specialized junctions, which also define cellular polarity. In addition, the presence of mucins and trefoil peptides, the rapid turnover of epithelial cells, and the peristaltic movement of the GI tract all help to protect against colonization and invasion of the intestinal mucosa by pathogens (Lievin-Le 2006). The role of increased epithelial permeability across the gut epithelial barrier (leaky gut) has gained increasing support in IBD pathogenesis, particularly as this epithelium represents an interface for genetic and environmental influences (Goyette 2007).

A compromised intestinal barrier may play a crucial role in the development of CD, by allowing the entry of luminal antigens and microorganisms into the mucosa and initiating overwhelming inflammatory responses (MacDonald 2005). A common feature of gut inflammation is increased epithelial permeability, both paracellular (i.e., the pathway between adjacent cells) and transcellular (i.e., material crosses through the apical and basolateral membranes) (Nazli 2006). One of the distinct features of CD is impaired intestinal epithelial function, characterized by increased permeability (altered barrier function) and ion secretion, often resulting in a luminally-directed driving force for water movement causing diarrhea. Interestingly, in otherwise clinically asymptomatic CD patients, increased intestinal epithelial permeability preceding clinical relapse has been observed, suggesting that a barrier defect may be an early event in disease reoccurrence.

Since first degree relatives of CD patients, without evidence of disease, also show abnormal intestinal permeability, it has been proposed that increased intestinal permeability may be a primary etiologic factor in IBD (Soderholm 2002). However, the inflammatory process itself leads to increased intestinal permeability (Bruewer 2003). Thus, it is not clear if these changes in the intestinal barrier integrity involved in the early events of IBD pathogenesis, or are simply a secondary phenomenon (Cobrin 2005, Targan 2005).

➢ **Intestinal microbiotics**: Interaction between genetics, immune function, permeability

Evidence supporting the hypothesis that in humans intestinal bacteria play a role in the pathogenesis of IBD includes 1) the observation that inflammation and lesions generally occur in intestinal regions with the highest bacterial concentrations (i.e. the terminal ileum and colon) (Thompson-Chagoyán 2005); 2) that IBD patients typically have greater numbers of adherent bacteria compared to normal subjects (Swidsinski 2002); and 3) diversion of the fecal stream can prevent intestinal inflammation whilst re-establishment of the flow will lead to recurrence (Fichera 2005).

There is likely an interaction between the intestinal microbiotics, and genetics, immune function and intestinal permeability. The microbiota then provides a constant stimulus for the host immune system (Shanahan 2004, Tannock 2005). Another hypothesis is that IBD develops due to an altered response to commensal bacteria, and not a pathogenic strain (Geier 2007). The associated lesions and the immunologic changes indicate a breakdown of mechanisms that maintain oral tolerance to components of the microflora and/or foodstuffs (Canny and McCormick 2008). The findings supporting the presence of an altered immune status include an exaggerated mucosal antibody response against intestinal bacteria.

In UC, particularly members of the genus Bacteroides are thought to play an important role in the development of intestinal inflammation: the rectal mucosa-associated bacterial flora in UC shows that both the highest bacterial counts and the highest isolation frequency were observed for B. vulgatus, Bacteroides fragilis, and Bacteroides ovatus, in that order (Poxton 1997).

Toll-like receptors (TLRs) are responsible for microbial recognition, induction of anti-microbial genes and control of the adaptive immune response (Cario 2005). There are a number of mechanisms to ensure tolerance, including a decreased surface receptor expression to limit recognition, and ligand-induced activation of peroxisome proliferators activated receptor-γ (PPARγ) which uncouple NFκB-dependent target genes (O'Neill 2006). TLR4 expression has been shown to be up-regulated in patients with IBD (Cario 2005).

The antibacterial peptides known as "α-defensins" are produced by Paneth cells at the base of crypts in the terminal ileum (Strober et al. 2007). CD patients with impaired NOD2 function manifest reduced α-defensin production, in part because NOD2 in Paneth cells is an inducer of α-defensin production. Thus, it is possible that impaired NOD2 function also leads to increased bacterial density in the crypts of the terminal ileum, and thereby greater stimulation of a mucosal immune system which is already set at a higher level of function.

4. Clinical Presentation

The course of CD is chronic, with recurrent episodes of inflammation, but not always associated with symptoms, complications, the need for hospitalization and possible surgery. The Vienna (Gashe 2000) and more recently the Montreal classifications are used to categorize the disease phenotype of CD and UC in a manner that has prognostic and therapeutic implications (Veloso 2001) (Tables 5, 6, and 7). The Vienna classification, and later, the Montreal classification, have both already been applied to Crohn disease populations in Canada but not for ulcerative colitis (Freeman 2001, Freeman, 2007).

Table 5. Summary of revised 'Montreal classification' of Crohn disease (Silverberg 2005)

o Age at Diagnosis (A)
   - A1 16 years or younger
   - A2 17-40 years
   - A3 Over 40 years

o Location (L)	o Upper GI modifier (L4)	
- L1 Terminal Ileum	- L1 + L4	- Terminal ileum + Upper GI
- L2 Colon	- L2 + L4	- Colon + Upper GI
- L3 Ileocolon	- L3 + L4	- Ileocolon + Upper GI
- L4 Upper GI		

o Behaviour (B)	o Perianal disease modifier (p)	
- B1* Nonstricturing, nonpenetrating	- B1p	- Nonstrictuing, nonpenetrating + perianal
- B2 Stricturing	- B2p	- Stricturing + perianal
- B3 Penetrating	- B3p	- Penetrating + perianal

*B1 category should be considered 'interim' until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg. 5-10 years is suggested) but should be defined in order for B1 behaviour to be considered 'definitive'. GI, Gastrointestinal.

Useful Practice Points:

A Simple Approach to Diarrhea

```
                    ┌──────────┐
                    │ Diarrhea │
                    └──────────┘
      ┌──────────┐              ┌──────────┐
      │ Acute <2 │──────────────│ Chronic >2│
      │  weeks   │              │   weeks   │
      └──────────┘              └──────────┘
                          ┌──────────┐  ┌──────────┐
                          │ IBS-D,   │  │ Organic  │
                          │ IBS-D/C  │  │          │
                          └──────────┘  └──────────┘
```
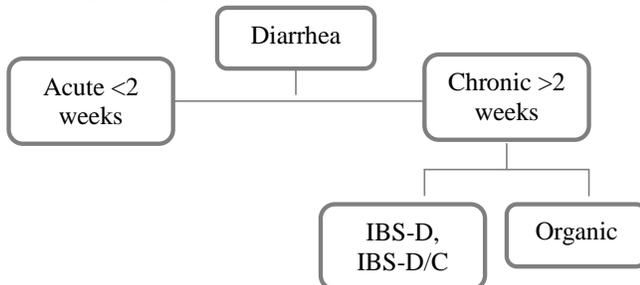
Note: IBS-D, IBS diarrhea predominant; IBS-D/C, IBD-diarrhea alternating with constipation; IBS-C, IBS-constipation predominant

Organic Causes of Chronic Diarrhea
  o Stomach- ZES, Rx, resection
  o Hepatobiliary-Jaundice, pruritus (cholestasis)
  o Pancreatic-alcohol, trauma, CF
  o SB-LV, "F's" foul, flush, fat, food, flatus
  o LB-SV, tenesmus, incontinence

Intestinal Causes of Chronic Diarrhea – The "I's"
  o Infection
  o Inflammation
  o Irritability
  o Ischemic
  o Infiltrative
  o Iatrogenic
  o Metabol-I-c

Diarrhea: IBD vs IBS: "Alarms"
  o Blood
  o Nocturnal
  o Weight Loss
  o Fever
  o Mouth, joints, skin, liver, kidney
     • Abdominal Mass
     • Perianal disease
     • Family history of IBD, CRC
     • Labs
        – CBC, ESR, CRP

- Electrolytes
- Stool cultures

Table 6. Montreal classification of extent of ulcerative colitis (UC) (Satsangi 2006)

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is porimal extend of inflammation is distal to the rectosigmoid junction
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Table 7. Montreal classification of severity of ulcerative colitis (UC) (Satsangi 2006)

Severity		Definition
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3	Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml and ESR of at least 30 mm/h

ESR, erythrocyte sedimentation rate.

There are differences between the child verus the adult with CD (Table 1). The cardinal symptoms include crampy abdominal pain, diarrhea (watery, may be bloody or may show signs of malabsorption), weight loss, fatigue, extraintestinal symptoms. There are clinical differences between CD and UC (Table 8).

The Montreal Working Party has recommended that the term ''indeterminate colitis'' should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either Crohn disease or ulcerative colitis after full examination (Silverberg 2005).

Table 8. Clinical features which are suggestive of CD rather than UC

- o Involvement of the terminal ileum; however, "backwash ileitis" occurs in 10-20% of UC patients, particularly extensive disease (Haskell H 2005);
- o Skip lesions; note that "cecal patches" are seen in 20% of UC patients (D'Haens G 1997);
- o Rectal sparing; however, this may be the beneficial effect of rectal 5-ASA/steroid enemas and;
- o The histological presence of granulomas is suggestive of CD, but these are also seen in 5% of UC patients (Lee 1997)

The severity of CD is assessed by clinical indices, such as the "CDAI", (Crohn disease Activity Index). The CDAI is heavily influenced by the subjective impact of symptoms such as abdominal pain, diarrhea, and poor sense of well-being (Best 1976). There is only a weak association between the patient's symptoms and the appearance of the bowel mucosa as seen by endoscopy, but there is a strong correlation between clinical indices and CD-specific measures of health-related quality of life (HRQOL).

QOL measures add important information on the person's emotional and social functioning (Bernklev 2004). These patient-reported outcomes (PRO) may be more valid and reliable than physician assessment outcome measures (FDA, 2006). The HRQOL is multi-dimensional, is reported directly by the patient, without "filtering" by the physician. HRQOL as well as other PRO instruments provide "…an integral picture of the interactions between a patient's disease, their treatment, and quality of life-positive effects resulting from the efficacy of a treatment and negative effects caused by adverse events..."(Rutgeerts 2008).

There are several useful, valid, reliable and easy-to-use PRO instruments, such as the Inflammatory Bowel Disease Questionnaire (IBDQ) (Bernklev 2004), the SNORT-Form 36-Item Health Survey (SF-36) (Bernklev 2005; Juan 2003; Welch 1995), the EuroQOL-5 dimensions (EQ-5D) plus health status visual analogue scale (VAS) (Cohen 2002; Casellas 1999, König 2002), and the Work Productivity and Activity Impairment-Specific Health Problem (Reilly et al, 1993), which has been adapted for persons with CD (Reilly 2006). These measures may be used to determine a normal life assessment, which combines measures of disease activity, HRQOL, work productivity and daily activity (Feagan 2009).

An important property of a PRO score is the MCID, the "minimal clinically important difference" (FDA, 2006; Mathias 2006). The MID, minimal important difference, is the smallest difference in a PRO score that patients perceive as beneficial, and that would indicate the need to change treatment (Coteur et al, 2009). In clinical trials, and reflecting everyday clinical practice, the MCID or MID are more important outcomes than small, unimportant yet possibly statistically significant changes in an activity index such as CDAI (Coteur 2009).

Extraintestinal manifestations (EIMs) occur in about 25-40% of CD and UC patients, especially if the colon is involved (Table 8). Erythema nodosum has many associations (Table 9), but in the context of CD or UC, it usually occursin the setting of disease activity.

Table 8. Extraintestinal manifestations (EIM) of IBD

EIM	Association with active IBD
o Erythema nodosum	90%
o Ocular inflammation	78%
o Large joint arthropathy (Type I)	80%
o AS, symmetrical small joint arthropathy (Type II)	independent extensive, but quiescent disease

Frequency of EIM, %	UC	CD
o Type I arthropathy	31	24
o Erythema nodosum	1	6
o Ocular inflammation	5	3
o Primary sclerosing cholangitis	2.4-7	0.7-12

AS, ankylosing spondylitis

(Jess 2006, Jess 2004. Ekbom 1990, Fireman 1989)

Patients with one EIM are more likely to develop another except that the patient with UC-associated primary sclerosing cholangitis (PSC) does not usually develop other extraintestinal manifestations (EIMs) (Orchard 2002). The usefulness of the EIMs is to anticipate other symptoms which the patient may develop and to treat those early and to recognize that some EIMs become symptomatic before the worsening of the bowel symptoms.

Table 9. GI causes of erythema nodosum

- o Inflammatory bowel disease (erythema nodosum usually occurs in the setting of gastrointestinal disease activity)
- o Behçet's disease (Ocular-oro-genital ulcers)
- o Infections: Strept throat, Salmonella, Campylobacter, Shigella (Diarrhea always present), Yersinia enterocolitica (Can mimic inflammatory bowel disease or occur without gastrointestinal complaints; probably rare outside of Northern Europe), HBV
- o Paniculitis (Skin lesions usually easily distinguished from typical erythema nodosum, and very rarely occur in advance of established diagnosis of pancreatitis)

Adapted from: Mirowski GW, and Mark L A. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006. page 450.

5. Diagnosis

The diagnosis of CD is made by the evaluation of compatible symptoms and signs, compatible hematological, serological, and biochemical blood tests, endoscopic, histopathological and diagnostic imaging findings, as well as exclusion of other pathologies (Panes 2007). These same features are used to differentiate between UC and CD (especially Crohn's colitis) (Baumgart & Sandborn 2007). Also, CD and UC must be differentiated from other causes of enteritis and colitis (Baumgart 2007).

> **Blood Testing, including Serological Markers**

The CRP (C-reactive protein) is neither sufficiently sensitive nor specific to be useful to make the diagnosis of IBD (Fagan et al. 1982), norto necessarily follow the clinical course. In known CD patients, high baseline CRP values may help to identify those who will respond to infliximab (Louis 2002).

Blood tests are useful to suggest possible active inflammation, as suggested by anemia, leukocytosis and thrombocytosis. Dehydration and electrolyte disturbances associated with vomiting or diarrhea may be reflected by abnormal primary (Na^+, K^+, Cl^-, HCO_3^-) or secondary (Ca^{2+}, Mg^{2+}) electrolytes, or elevated serum urea or creatinine.

On immunofluorescent staining, the IBD-specific antineutrophil cytoplasmic antibody (ANCA) has perinuclear highlighting (pANCA), and is DNAse sensitive (Duerr H 1991). IgA and IgG antibodies to saccharomyces cerevisiae (ASCA) are seen in less than 5% of the non-IBD population, in ~10% of UC patients, and in ~60% of those with CD (Ruemmele 1998). A third of asymptomatic persons positive for ASCA will develop CD within a mean of 38 months (Vidrich 1995).

In about half of CD patients (but not in UC or healthy controls) there are serum antibodies to the *E. coli* outer membrane porin C (OmpC), the Pseudomonas fluorescens CD-related protein (I2), and the anti-flagellin (CBCR1) marker. A combination of these markers may help to support but not make a diagnosis of UC or CD, or to distinguish between the two (Dubinsky et al. 2002). Double-positive combinations are also potentially predictive (Peeters et al. 2001, Quinton et al. 1998, Joossens et al. 2002); for $pANCA^+$ / $ASCA^-$, there is a PPV of 90% for UC, and predicts that 64% persons with IBDU (IBD unclassified) will later evolve into a picture which is compatible with UC. For the combination $pANCA^-$ / $ASCA^+$, there is a PPV of 90% for CD, this combination ($pANCA^-$ / $ASCA^{+)}$ predicts that 80% of persons with IBDU will develop CD. There is also a predictive factor for triple-positive combinations: CD patients who are positive for ASCA, anti-OmpC, and anti-I2 are more likely to require small bowel surgery (OR, 8.6: p<0.001) (Mow 2004).

Children with CD who are immunoreactive against multiple microbial antigens are more likely to develop penetrating or structuring disease (Dubinsky 2006). These serological markers may also be useful to predict clinical course and therapeutic response. For example, a higher pANCA is predictive of chronic pouchitis post-IPAA (Fleshner et al. 2001). A higher ASCA – anti-OmpC, anti-I2, or anti-Cbir 1, are predictive of an earlier age of CD onset, structural and penetrating disease, or the need for future small bowel surgery (Vasiliauskas 2000, Mow 2004, Targan 2005). pANCA, ASCA, OMPC and Cbir 1 are not necessary for the diagnosis of IBD (Sandborn 2004), but may help to confirm the diagnosis made by other means (Kane 2008). ASCA, OMP-C, Cbir -1 may be associated with complicated small bowel disease (Dotan 2006).

Table 10. Sensitivity, specificity, PPV and NPV of serological markers in persons with Crohn disease or UC

Marker	Diagnosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ASCA	CD	50-65	70-85	80	64
pANCA	UC	65-80	70-85	64	80

Adapted from: Targan SR. *AGA Institute PostGraduate Course book*. page 47.

Genetic testing with NOD2/CARD15 is not recommended as a diagnostic test (Vermeire 2004), "as the likelihood of a positive test in patient without the appropriate family history, or a negative test in a patient with appropriate signs and symptoms, is still relatively unknown and the results will be misleading (Kane 2008).

➢ **Fecal tests**
The presence of white blood cells (WBC) in the stool is supportive of an inflammatory process, but is neither sensitive nor specific for the diagnosis of IBD. Stool cultures need to be performed to exclude infectious causes of colitis or infectious causes of symptoms in persons with known CD or UC. Stool cultures should always include C. difficile, even in the person who has not recently been on antibiotics, and include cytomegalovirus (CMV) in the immunocompromised individual. Some persons with CD may need 72-hour stool collections to assess for possible fat or bile acid malabsorption.

➢ **Urine tests**
Urine calprotectin and lactoferrin are sensitive markers for inflammation in general, but are not specific for IBD. A stool calprotectin greater than 10mg/L predicts organic disease, with a sensitivity of 89% and a specificity of 79% (Palmon 2008). An elevated stool calprotectin or lactoferrin level > 7 mg/mL is 100% sensitive and 85% specific for pouchitis in the person who has had a colectomy and IPAA (ileal pouch anal anastomosis) (Parsi 2004, Johnson 2008).
The increased excretion into the urine of orally injested compounds (such as mannitol, lactulose, sucralose, PEG [polyethylene glycol], chromium or EDTA) may be used as markers of intestinal permeability. This increased intestinal permeability in active CD reflects increased intestinal inflammation (Parrilli 2006). When there is increased intestinal permeability in a person with CD who is clinically well, there is an increased risk of their suffering a clinical recurrence within one year (Vogelsang 2008), with a positive predictive value (PPV) of 44-75%, and a negative predictive value (NPV) of 46-49% (Vogelsang 2008).
Because intestinal permeability may be enhanced by much more than small intestinal CD (eg NSAIDs, alcohol, infections), these tests are too non-specific to be used for diagnostic purposes, but in a research setting may be useful to predict the presence of subtle disease activity.

➢ **Diagnostic Imaging and Endoscopy**
It is unclear what is the sensitivity and specificity for the diagnosis of CD using upper GI barium series, small bowel follow-through, air contrast barium enema, CT colonoscopy or enteroscopy, MRI or MRI enteroscopy, endoscopic ultrasound (EUS), optical colonoscopy, enteroscopy, esophagogastroduodenoscopy (EGD), colonoscopy with intubation of the terminal

ileum, push or double-balloon enteroscopy, or video capsule endoscopy. Colonoscopy is an important procedure to be performed in persons with CD and UC (Table 11).

Useful Practice Points:

➢ If IBD is suspected: If you "Imagine," then "Image"
- o Ulcerative Colitis (UC) $100/10^5$
- o Crohn's Disease (CD) $200/10^5$
  - − Ileum 40%
  - − Il + C 40%
  - − Colon 20%
  - − Imaging
    - ▪ ACBE ± sigmoidoscopy/colonoscopy
    - ▪ Small bowel (FT, enteroclysis, CT, MRI)

➢ Distinguishing IBD from IBS
- o Demography

	IBD	IBS
− Young Female	3/103	3/101
− Alarms	++	-
− Labs	++	-

➢ Why distinguish between UC and CD
- o Acute-targeted 5-ASA; CYA; surgery
- o Maintenance-5-ASA for UC, AZA for CD
- o Steroid resistant AZA for UC/CD TNFβ
- o Nutritional complications
- o CRC surveillance (CD-C involvement)
- o Type/timing of surgery

Table 11. Indications for colonoscopy in patients with IBD

- o Differentiating IBD from other diseases, and differentiating Crohn's from ulcerative colitis
- o Establishing the extent of the disease, and any complications (fistula, strictures)
- o Evaluation of abnormalities on radiographs
  - - Strictures
  - - Masses
- o Evaluation of disease not responsive to standard therapy
- o Therapeutic applications
  - - Bleeding control
  - - Dilation of strictures
  - - Obtaining biopsies
- o Screening for malignancy and malignant precursors

It is important to note that in 2.6-24% of persons given oral sodium phosphate solution for preparation of a colonoscopy, aphthous ulcer-like colonic ulcerations may be seen which may be confused with CD (Preiksaitis 1998).

The earliest intestintal radiological lesions in seen CD are tiny aphthous ulcers, and later large ulcers develop (Figure 1).
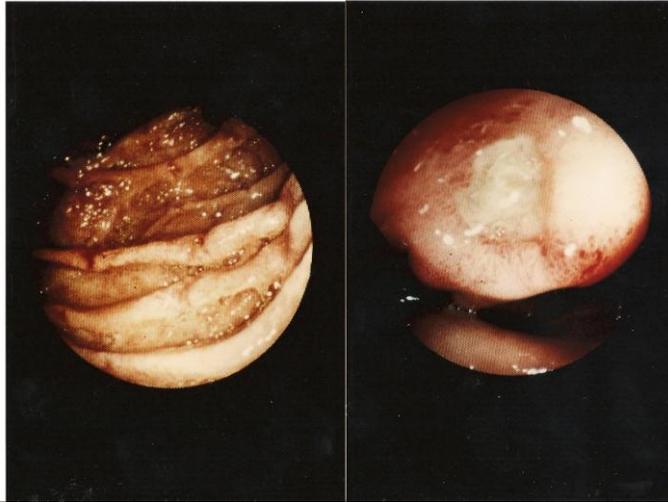
Figure 1. These are stelate-shaped, serpiginous or deep, and may give a cobblestone appearance on barium x-rays.

Figure 2. A small bowel CT finding in CD include abnormal thickening of the bowel wall, perienteric stranding, and intra-abdominal abscesses (Hellers 1999). EUS and MRI are particularly sensitive to detect perirectal and perianal fistulae, as well as abscesses. CT enterography/enteroclysis as well as MR enterography, with or without gadolinium, show promise for the diagnosis of CD and its complications (Masselli 2004).

> **Histopathology**

The key diagnostic test to establish IBD from non-IBD conditions is the histopathlogy of mucosal biopsies obtained at endoscopy, or full thickness biopsies obtained from surgical or autopsy speciments (Yusoff 2002). The cardinal histological features of IBD are 1) architectural distortion (including crypt distortion [non-parallel, variable diameter, cystic crypts]), crypt branching, shortening, decreased density, irregular mucosal surface; 2) inflammatory features – increased lymphocytes or plasma cells between the bases of the crypts and in or close to the muscularis mucosae (Kane 2008) (Figure 3).
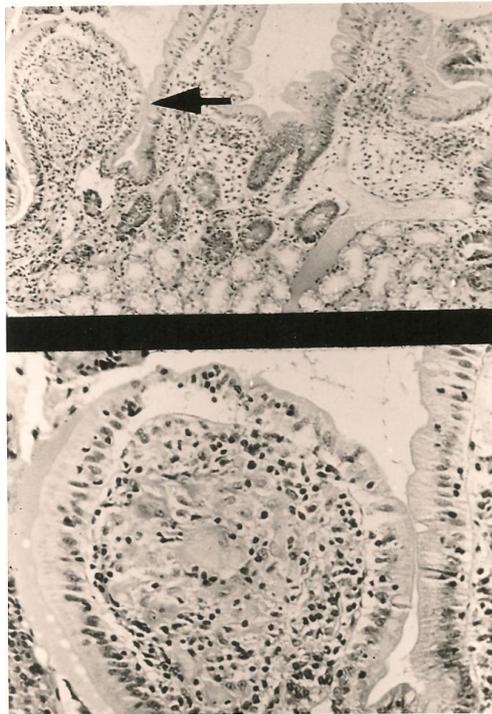
Figure 3. Microscopic mucosal granuloma in an endoscopic biopsy from the duodenum of a patient with Crohn disease.

There are usually more plasma cells on the right versus left side of the colon; and 3) metaplasia: pseudopyloric metaplasia in the ileum, as well as Paneth cell metaplasia (in especially on the left side of the colon). While granulomas may be detected in up to a third of persons with Crohn disease, their presence of granuloma is not necessary to make the diagnosis of CD. Detection of granulomas in biopsies or surgical specimens, however, may reflect an earlier stage in disease course or pathogenesis (Freeman, 2007). These histological features help the pathologist to distinguish between UC and CD of the colon (Geboes 2008) (Tables 12 and 13).

Table 12. Histological features which favour CD

- o Patchy crypt architectural changes
- o Patchy inflammation
- o Mucin at sites of active inflammation
- o Irregular muscularis mucosae
- o Cryptitis
- o Epithelial Granulomas
- o Fissures
- o Transluminal lymphoid aggregates
- o Transmural disease
- o Submucosal nerve fiber hyperplasia with ganglionitis

Table 13. Histological features which favour UC

- o Severe, widespread distortion
- o decreased crypt density, and irregular crypt surface
- o heavy, diffuse, mucosal lamina propria cell increase
- o Paneth cell metaplasia in biopsies taken distal to the hepatic flexure
- o Thickened but not irregular muscularis mucosae

There is diagnostic variability in the accuracy of pathologists in distinguishing UC vs. CD. In CD, the diagnostic accuracy of the pathologist is 60-74%, with difficulty experienced in making this distinction in early, treated or fulminant disease (Bentley 2002). Transmural lymphoid aggregates (specificity, 90%; PPV, 62%), granulomas in the subserosa unrelated to mucin or foreign bodies, fissures, transmural disease, submucosal nerve fiber hyperplasia with gaanglionitis all favour CD (Swan 1998). On the basis of histology, biopsies give the diagnosis of CD and UC in 64% and 74%, respectively, in UC, increasing to 96% with additional clinical information and supporting evidence (Bentley 2002).

UC and CD must be distinguished from acute self-limited (infectious-type) colitis (ASLC) (Table 14), in which the patient may have the same symptoms as IBD, including extraintestinal symptoms such as iritis, episcleritis, arthropathy, pyoderma, gangrenosum, and erythema nodosum (Surawicz 2008).

Table 14. Histological features on mucosal biopsy of acute self-limiting colitis (AC) which help to distinguish it from chronic idiopathic ulcerative colitis (UC)

Histopathological feature	ASLC	IBD
o Crypt distortion	-	+
o Inflammation	Acute	Acute/chronic
o Increased plasma cells or lymphoid aggregates at crypt bases	-	+
o Granulomas	Only with crypt abscesses*	+
o Pyloric metaplasia in the terminal ileum	-	+
o Paneth cells in the left side of the colon	-	+

*crypts are straight, parallel and close, possibly with bulging and a "necklace of cells" around any crypt abscess

There may be an elevated WBC count in ASLC, but stool cultures are positive in only about half of persons with suspected bacterial colitis. Clostridium difficile-associated disease (CDAD) may occur by itself, or in association with IBD, when it may be severe (especially in persons with colonic disease or who are on immunosuppressants), and the typical pseudomembranes may be absent on sigmoidoscopy or colonoscopy (Issa et al. 2007, Rodemann et al. 2007), so the possibility of CDAD always needs to be considered and excluded by stool culture. Infectious colitis may be patchy, enteritis may occur, and colonic ulcers may also occur (especially with tuberculosis and amebiases), although the sarpiginous ulcers of CD are not usually seen). The colonic biopsy is the best test to distinguish between IBD and ASLC in the adult.

These typical histological features for the adult with IBD may be different for the child: crypt distortion is less common (only 34%) (Robert 2004), yet rectal sparing and patchy involvement is more common (26% and 21%, respectively) (Glickman 2008). Also, these histological features may be different for the adult or child who presents with fulminant colitis (UC or Crohn's colitis), where there may be fissures, transmural inflammation, and rectal sparing. Local enema/suppository therapy may result in rectal sparing. In acute colitis there may be patchy disease (59%) (Kleer 1998), as well as fewer histological features of chronicity such as basal lymphoid aggregates or basal plasmacytosis.

Useful Practice Points:

Is it important to distinguish between Crohn disease and Ulcerative Colitis?

- o   Crohn—Mouth to anus:
- ➤ Different complications in Cronh disease
    - -   Malabsorption
    - -   RLQ Mass
    - -   Perianal disease
    - -   Fistulae
    - -   Skip Lesions
    - -   Bleeding
    - -   Dilation

- o   Ulcerative Colitis:
- ➤ Different treatments
    - o   Acute
        - −   UC-CyA or CyA
        - −   CD-CyA not effective
    - o   Maintenance
        - −   UC-5-ASA (not effective in CD)
        - −   CD-AZA/MTX
    - ➤   Surgery

Abbreviation: AZA/ MTx, Azathioprine/ methotrexate; CD, Crohn disease; CyA, cyclosporin A; RLZ, right lower quadrant; UC, ulcerative colitis

---

> ➤ **How often is a diagnosis of UC changed to CD, and vice versa?**

About 10% of patients who are diagnosed with colonic IBD may initially not have sufficient diagnostic features to make a firm diagnosis of UC or CD (Meucci 2008). These persons are considered to have "indeterminant colitis" or IBD unclassified (IBDU) (Gebos 2008). When surgical specimens are used for diagnostic purposes and the diagnosis of the type of IBD is unclear, the term "colitis of uncertain type or etiology (CUTE)" is used. Over time, about one third of IBDU patients are re-classified as CD, 1/3 as UC, and the rest remain IBDU (Burakoff 2004). Over time, about 3% of persons with CD are reclassified as having UC, and 3% of UC patients are reclassified as having CD (Moum 1997).

Capsule endoscopy (CE) is proving to be useful to identify persons as having small bowel abnormalities. In the person who is thought to have UC and CE shows small bowel lesions, the diagnosis likely needs to be changed to CD (Mow 2004). In persons initially thought to have UC and who have an IPAA, about 4% are reclassified to CD (Yu 2000). Pouch failure occurs in as many as 30% of these CD patients who were misclassified as having UC (McLeod 2002).

Useful Practice Points:

> ➤ Is the diagnosis of IBD correct?
> - o   Suspect diagnosis from symptoms and signs (GI, non-GI)
> - o   Compatible x-ray or endoscopic changes
> - o   Compatible or diagnostic biopsy
> - o   Indeterminate, UC, Crohn's
> - o   For some, only time will tell

---

6. Clinical Course

At the time of diagnosis of CD, the terminal ileum is involved in ~47%, colon alone in ~28%, ileocolon in ~21%, and the upper GI tract (Jejunum, duodenum and stomach) in ~3% (Louis 2001). This distribution remains relatively stable over time. At the time of diagnosis of CD, ~70% have non-stricturing, non-penetrating (ie. inflammatory CD), ~17% structuring, and ~13 % have penetrating disease (fistulae or abscesses) (Louis 2001). Over a 10-year interval, of those persons who were initially diagnosed with the "inflammatory" form of CD, ~27% progress to stricturing and ~29% to penetrating disease (Podolsky 2002). A longer term study explored the natural history of Crohn disease over more than two decades and confirmed that the behaviour of Crohn disease progresses from a largely inflammatory process to a more complex disorder complicated by stricture formation and penetrating or fistulising disease complications (Freeman 2003). However, the clinical course may also have prolonged asymptomatic periods, often for more than a decade, before symptomatic recurrence is defined (Freeman, 2003). This may have implications for the clinical management of patients with Crohn disease where critical evaluation of treatments suggested for prevention, rather than control of symptoms is needed.

The rate of hospitalization for CD is about 20% per year (Berstein and Nabalamba 2006). About 53-57% of the cost of the disease is due to hospitalization, especially for surgery (Juan 2003). A quarter of CD patients are unable to work fully one year after onset of their CD, and

15% after 5-10 years (Carter et al.2004). Over the lifetime of the CD patient, 75% will require surgery (Carter 2004), and 25% require surgery within 10 years of diagnosis (Stange et al.2006). Mortality rates for persons with CD are either similar to that of a general population (Jess 2006), or are slightly increased, especially in younger persons, who ten to have more severe diseases (Wolters 2006).

One year after diagnosis, 10-30% have had an exacerbation of their symptoms, 15-25% have low disease activity, and 55-65% are in remission. Thereafter, between 13 to 20% of CD patients have chronic active disease, 67-73% have chronic intermittent CD, and 10-13% remain in remission for several years (Loftus 2002) (Table 15).

After surgical resection for failure of medical therapy, endoscopic recurrence is early and rapid (73% at 1 year, 85% at 3 years), with symptoms occurring later (1 year, 2%, 3 years, 34%) (Schwartz et al.2002). It is unknown why there is this disconnect between active inflammation and symptoms. While improvements of the patient's symptoms (as reflected in an activity index such as CDAI and quality of life) are desirable outcomes, the longterm focus needs to be healing of the underlying inflammation (and of course, to discover the cause of CD).

Table 15. Comparison of the Clinical Course of CD and UC

	UC Course	CD Clinical Course 1 year after diagnosis	
o Clinical remission at any point in time	50%	Relapse	10-30%
o Overall Intermittent course	90%	Low Activity	15-20%
o 3-7 years after diagnosis in remission	25%	Remission	55-65%
o Yearly Relapse	18%	Chronic Active	13-20%
o Intermittent Relapse	51%	Chronic Intermittent	67-73%
		Remission for 10 yrs	13%
o 10 year Colectomy Rate	10%	Surgery by 20 yrs	>75%
o Change in site of involvement over 25yrs		Change in behavior NSNF → S 27 % NSNF → F 29 %	

Abbreviations: F, fistulizing CD; NSNF, non-stricturing and non-fistulizing; S, stricturing
    (Baumgart 2007)

> **Triggering Factors for relapse**

Both CD and UC have chronic recurring clinical courses. A recurrence of symptoms ("flares") does not necessarily indicate recurrent inflammation, and the severity of symptoms does not reflect the severity of underlying inflammation.

In the patient with known IBD who presents with a recurrence of symptoms, the symptoms may be related to an incidental infection such as giardiasis, CMV or Cl. difficile, small intestinal bacterial overgrowth, a drug reaction (eg NSAIDs, 5-ASAs or antibiotics), food intolerances such as milk, bile acid induced diarrhea due to partial interruption of the enterohepatic circulation, or associated IBS-like symptoms. A recurrence of symptoms due to a recurrence of the IBD may be related to stopping maintenance medications, changing smoking habits, pregnancy, and possibly stress.

Clostridium difficile-associated disease (CDAD) may occur in association with IBD. It may be severe (especially in persons with colonic disease or who are on immunosuppressants), and the typical pseudomembranes may be absent on sigmoidoscopy or colonoscopy (Issa et al. 2007, Rodemann 2007). Thus, the possibility of CDAD needs to be considered and excluded by stool culture.

In some persons, stress and distress do affect the ups and downs of IBD symptoms and/or inflammatory activity, as well as being a factor which may influence the patient's disease experience (Levenstein 2008). The psychosocial aspects of the patient's care are of great importance in the therapeutic relationship between the physician, the patient, and the person in the patient. "Quality of life is improved in those receiving quality professional care and guidance, and by strong peer and family support, as provided by the patient's informed and understanding physician, health care personnel and family" (Moser 2008).

Useful Practice Point:

➢ Even patients with IBD have IBS-like symptoms
  o IBS-like symptoms shouldn't be treated as IBD
    – Anti-diarrheal agents
    – Anti-cholinergics
    – Anti-biotics
    – Bile acid sequestrants
    – Analgesics
    – Exercise caution when/if using analgesics

---

7. Management
➢ General Principles

In a research setting the efficacy of a treatment for CD is often reported as a change in the score of the Crohn disease activity index (CDAI) by a given number of points (eg. 70 points, a "response") and a reduction in the CDAI to or below a given value (eg. 250, "remission"). However, there are a number of often important goals to achieve with therapy in CD (Table 16). Understanding the rationale of the different management of persons with CD requires an appreciation of the natural history of the disease. Therapeutic efficacy is balanced against adverse effects and costs (both direct and indirect). Induction of remission in this context is based on symptom improvement, with only anti-TNF therapy being reliably associated with endoscopic healing (Rutgeerts 2006, Hommes 2006). This in turn may be associated with reduced time-to-time relapse (D'Haens 2002), as well as a decline in IBD-associated hospitalization and the need for surgery at one year (Rutgeerts 2006).

Useful Practice Points:First Line Therapy for IBD

➢ Diagnosis   ➢ Complications
➢ Information   o N utrition
➢ 5-ASAs   o O steoporosis
                     o P sychological

Table 16. Goals of Therapy in CD

- o Cure the disease (not yet possible)
- o "normal life"-quality of life (QOL)
- o normal mental health
- o Induction and maintenance of clinical remission of intestinal and extraintestinal symptoms
- o Endoscopic and histopathological remission
- o Normal nutrition
- o Normal ability to got to school, to work, to raise a family, to enjoy leisure time and to be free of worry about the financial costs of their disease

---

Useful Practice Points:

- ➢ Ask yourself a few questions:
  - o Is the diagnosis of IBD correct?
  - o Are you prescribing the right 5-ASA preparation?
  - o Are you using GCS appropriately?
  - o Should an immunosuppressant be used?
  - o Why are you not using an immunosuppressant?
  - o Is there a good reason to use biological therapy?

Patients with IBD need accurate information about their condition, they must have a sense of control over themselves and their illness, and like all of us, they need strong social support (Moser 2000, Moser 1996, Sewitch 2001, Kennedy 2004). For example, denial and social withdrawal, as a means of coping with depression have a major negative impact on the person's quality of life, and possibly also on the disease process itself (Janke 2005, Mussell 2004). Thus, it is important to incorporate psychological care into the management of persons with IBD.

Part of the therapeutic discussion in CD includes a review of the diagnosis, and the exclusion of precipitating factors; the informing of the patient that in a small proportion of persons, the initial diagnosis of CD may be changed to UC, or UC to CD; that every treatment may ahve adverse effects; that there are a number of therapeutic options; that surgery may be an option, and that there is a risk of colon cancer in persons with Crohn's colitis or UC, and of small bowel adenocarcinoma and lymphoma in CD.

As best as possible, therapeutic discussion must be evidence-based, yet modified carefully by the included needs of the patient. Physicians must recognize the potential bias in their therapeutic choices for patients, based on their interaction with the pharmaceutical industry (Wazana 2000).

In order to fully appreciate the therapeutic gains of various treatments in persons with Crohn disease (CD), it is useful to appreciate that about 25% of CD patients with an attack (flare) of acute CD disease will go into remission, without the use of active therapy (ie placebo response), and about 33-50% will remain in remission, even when not on maintenance therapy.

An attack or relapse of CD is considered to occur when the CD symptoms flare (as indicated, for example, by an increase in their CDAI as reflected by symptoms of pai, diarrhea, loss of sense of well-being, abdominal tenderness), in association with an elevation of markers of inflammation (decreased hemoglobin concentration; increased WBC, platelets, ESR, CRP);

characteristic changes in endoscopy, and diagnostic imaging, histopathology and possibly increases in fecal lactoferrin or calprolectin or increased intestinal permeability assessed by lactulose/mannitol urinary excretion test. It must be stressed that therapeutic trials of drugs used in CD and UC have focused on the improvement of symptoms, or QOL. Several systems have been developed to score the endoscopic severity of C, but there is a poor condition between the endoscopic and clinical scores of activity, or biological markers of activity such as CRP. The issue of the importance of mucosal healing remains unclear.

Useful Practice Points:

➢ What to do when Symptoms Come Back: Is this IBD, or Something Else?
  o Infection
  o Pregnancy
  o Drugs
  o Other conditions (stress)
  o Non-adherence to maintenance Rx
  o Change in smoking habits

➢ Is this a Severe Recurrence of Symptoms?
  o > 6 BM/day
  o Blood
  o Pain, malaise
  o Fever
  o Extraintestinal symptomizing arthralgias, Aphthous Ulcers, rash

➢ Is this a recurrence of IBD?
  o 3-day D/C 5-ASA
  o Double dose 5-ASA
  o Start prednisone 40 mg (AEs) for 2 weeks, then taper
  o Call your "GI" , "GIM", or "GS"
    – If no response, or quick return of symptoms with taper:

➢ What will the referral MD likely do?
  o Confirm the diagnosis
  o R/O
    – Infections (stool cultures)
    – Obstructions (abdominal film)
    – Abscess (ultrasound, MRI)
  o Full dose 5-ASA, start on prednisone
  o Judicious decision re: "scoping"
  o Consider immunosuppression

> "Tips on staying on top®" of IBD
>   o Causes of chronic diarrhea
>   o Distinguish between
>   − IBS & IBD
>   − UC & CD
>   o First line therapy for UC, CD
>   − 5-ASA
>   o Maintenance 5-ASA
>   o What causes recurrence of symptoms
>
> Abbreviations: AE, adverse effects; D/C, discontinue; GI, gastroenterologist; GIM, general internal medicine specialist; GS, general surgeon

Nutritional assessment is of utmost importance in the care of of the patient with IBD. A major later section is dedicated to this topic.

Table 17. Evidence Based Recommendations for therapy in IBD

Medication	Indication	CD	UC
➢ 5-ASA	o Induction	No (2c)	Yes (1B)
	o Maintenance	No (2c)	Yes (1A)
➢ Corticosteroids	o Induction		
	− Standard	Yes (1c)	Yes (1c)
	− Budesonide	Yes (1c)	No
	o Maintenance		
	− Standard	No	No
	− Budesonide	No (2c)	No
➢ Antibiotics	o Induction		
	− Inflammatory	No (2d)	No (2d)
	− Fistulizing	Yes (2c)	
	o Maintenence	No (2d)	N/A
➢ AZA/6-MP	o Induction	No (2c)	No (2d)
	o Maintenance	Yes (2c)	Yes (2c)
➢ MTX	o Induction	Yes (2c)	No (2d)
	o Maintenance	Yes (2c)	No (2c)
➢ CyA	o Induction (IV)	No (2d)	Yes (2d)
	o Maintenance	No (2c)	-

Medication	Indication	CD	UC
➢ TNFB	o Induction		
	− Inflammatory	Yes (1b)	Yes Ambulatory (1b) Hospitalized (2d)
	− Fistulizing	Yes (1c)	
	o Maintenance	Yes (1a)	Yes N/A
➢ Anti-α 4integrin antibodies	o Induction o Maintenance	Yes Yes	- -

A, high quality evidence; 5-ASA, 5-aminosalicylic acid; B moderate-quality evidence; C, low-quality evidence; 95% CI, 95% confidence interval; D, very low-quality evidence; IV, intravenous; N/A, not applicable; NNH, number needed to harm; NNT, number needed to treat; UC, ulcerative colitis; 1, strong recommendation; 2, weak recommendation.
[aNNT] should NOT be compared between therapies, as trials evaluated different severities of disease and used different end points to define remission, bNNT for symptom improvement and not remission.

Adapted from: *The American Journal of Gastroenterology* 2011; 106: S1; doi: 10,1038/ ajg.2011.79

o **Accelerating the induction of remission of inflammatory CD**

Much of the practice of the care of the patient with severe active CD is derived from data from severe UC. This management will be reviewed here, as well as in the chapter on UC. About a third of UC patients will require therapy with glucocorticosteroids (GCS, "steroids") (Faubion 2001), and one in six UC patients will have a sufficiently severe flare that they will require hospitalization (Truelove 1955). This severe attack may occur when the diagnosis is first made, or at a time when the UC patient's flare becomes progressively more severe and does not respond to oral GCS. Unlike UC, cyclosporine (CyA) is not effective in persons with sever and active disease.

The use of AZA/6-MP is not an option in the acute setting, because of the effect of immunosuppression takes in 8-12 weeks of therapy. If the patient who has more than one flare per year while being adherent to taking maintenance doses of 5-ASA, the use of AZA/6-MP needs to be considered. The probability of an IBD patient remaining in remission increases over time, so that the longer they are in remission, the more likely they are to stay in remission.

o Sulfasalazine (SASP) and Mesalamine (5-ASA)

SASP (Sulfasalazine) has a modest effect in active CD of the colon, especially if given to GCS-naïve patients, or when the SASP is given with GCS (Summers 1979, Van Hees et al. 1981). The evidence is weak for 5-ASA (mesalamine) being efficacious for acute CD, with NNT (number-needed-to-treat) being relatively high. (Meta-analyses of 5-ASA in active CD: has shown a statistically superior to placebo, but the 18 CDAI [Crohn disease activity index] unit difference is not statistically meaningful (Hanauer 2004).

The 5-ASAs have different release patterns from their formulations, with the purpose of targeting particular parts of the gastrointestinal tract (Table 17). They are often given 3 to 4 times a day, but MTX for example is effective when given once a day. This once a day dosing is good for the patient, may improve their compliance with the medication, and their quality of life. Even though SASP / 5-ASA have many potential mechanisms of action (reduction of the function of prostaglandins and leukotrienes, reduction in cytokine and free radical production, reduction of leucocyte function and adhesion) (Novak et al. 2008), their actual means of achieving efficacy in UC or CD is unknown.

Table 18. Anatomical location of the release in the GI tract of orally administered 5-ASA products

- o Mesalsal®/Salofalk®: terminal ileum (pH > 6)
- o Asacol®: terminal ileum; cecum (pH > 7)
- o Pentasa®: release begins in jejunum
- o Dipentum® and sulfasalazine: colon (diazo bond)
- o Balsalazide® (available in the USA): colon
- o Generic 5-ASA (modeled after Asacol): terminal ileum, but may be released at pH 5.5 (in proximal GI tract which is the problem with it)
- o MMX (once a day) – colon

Useful Practice Points:

- ➢ 5-ASAs for IBD
  - o Mesalamine
    - – Plus sulfa
    - – Plus coating
  - o Release pattern
    - - P .O.   SB+C   Pentasa
    - - TI   Salofalk
    - - C   Asacol (400 mg)
    - - P .R.   Enemas (4 g), suppositories (500 mg)

- ➢ Choosing a 5-ASA product
  - o Adverse effect
    - – SASP 30%
    - – Mesalamine 1 to 5%
  - o Dosing
    - – QID-TID-BID-once a day!
  - o Route
  - o Cost
  - o Theoretical Differences

- ➢ Use of Mesalamine in IBD
  - o Acute 4 g P.O., P.R.
    - – Caution: slow onset, long duration
  - o Maintenance 2 g
    - – UC ⎤
    - – CD ± (limited use)
    - – For life

Useful Practice Points:

Are you prescribing the right 5-ASA preparation?
- o   Mesalamine vs Salazopyrine-cost, AEs
- o   PO-dose, duration, target site
- o   Local-enemas, suppositories ± PO

Individual studies may suggest that mesalamine may be useful maintenance therapy after surgery for the patient with CD. For example, Asacol®, the pH 7-dependent 5-ASA, reduces the risk of recurrence of CD after surgery (Steinhart 2007). Unlike the efficacy of mesalamine (5-ASA) in UC, 5-ASA has only a modest benefit (10%) of maintaining a medically-induced remission in CD (Cammà 1997) (Edwards). However, in meta-analyses, 5-ASA has a slightly better effect (NNT, 10) maintaining a surgically-induced remission of CD (NNT, 10) (Cottone 2000).

Sulfasalazine (SASP) use is associated with mostly minor adverse effects (AEs) in about one person in four. Reversible sperm abnormalities are common in men taking SASP. The AE profile of mesalamine is less than 5% (Loftus 2004), and only 10-20% of persons intolerant to SASP show the same AEs with 5-ASA (mesalamine) (Scribano 2008). There is no clear dose-response relationship between 5-ASA AEs, and therapeutic response, but there may be a dose threshold to achieve clinical efficacy (Mansfield 2002). Some clinicians find that taking 5-ASA/SASP medications with food, and gradually increasing their dose will help to establish better patient tolerance. Interstitial nephritis is rare with chronic (maintenance) use of 5-ASAs. Adding topical (enema) 5-ASA is useful for the person with left-sided colonic disease, and continuing the oral with the topical (enema) therapy provides added benefit (Marteau 2005).Persons with impaired renal or hepatic function may need to avoid 5-ASA compounds. The 5-ASA drugs increase the value of the patient's INR, as well as increases the blood concentrations of 6-TGN and methotrexate, and decreases digitalis levels; allopurinal increases 6-TGN; and ACE inhibitors increase the 6-MP-associated risk of anemia, and leucopenia.

o   Glucocorticoids (GCS)

About 43% of CD patients will require GCS (Faubion et al.2001). Treatment with GCS indicates worsening of the disease severity, with 38% requiring surgery and 28% becoming steroid-dependent (Knutson 2003).

There is sound evidence to support the short-term use (no more than 4 months) of GCS in the patient with symptomatically active CD (Summers 1979, Malchow 1984, Modigliani 1990). The NNT for steroids in CD is only 2. Longterm steroid maintenance is without benefit, is complicated by adverse effects, and must be avoided. Because of the common and/or serious adverse effect profile of GCS, this point needs to be emphasized: do not use GCS for long trm use in persons with CD.

In persons with a non-severe flare who do not respond to the full flare-dose of 5-ASA, GCS are introduced at a dose of prednisone 40 mg/day for mild and 60 mg/day for moderate disease activity. Be certain to warn the patient and record in the medical record the fact that you have discussed with the patient the many adverse effects of using GCS. Expect that about three persons in four will begin to respond to GCS within two weeks. When there is a convincing clinical response, begin to slowly taper the prednisone at the rate of one 5 mg tablet per week (e.g. 40 mg/day, then 35 mg per.day for one week, then 30 mg/day for one week etc). Once the patient has tapered down to 15 mg/day, slow the rate of taper to even further one half a 5mg tablet (ie. 2.5mg) per week. This is the time to discuss with the patient the pro's and con's of maintenance (continuous) therapy with some other agent (ie, do not use GCS long term).

In the outpatient setting, oral prednisone will achieve clinical remission in 60-70% of patients (Braegger 1992). When UC patients do not respond to oral therapy, steroids may be efficacious with IV therapy (Jarnerot 1985). This is presumably also true in CD.

Steroid dependence (continued need to use GCS because of relapse with dose reduction, or a relapse within 3 months after tapering GCS) occurs in 28-36% of CD and 22% of UC patients (Faubion 2001, Munkholm 1994). Steroid resistance (failure to respond to GCS) is also common, and the mechanisms are complex (Table 18). Only about 29% of CD patients achieve mucosal healing with GCS (Modigliani 1990). The importance of mucosal healing as a therapeutic objective is only now becoming recognized.

Entocort® is coated budesonide target for ileocolonic release. For terminal ileal and/or right-sided colonic CD, Entocort® is similarly efficacious as prednisone, with a much lower risk of steroid-related adverse effects. Entocort® used in CD for up to 12 months increases the time to relapse, but should not be used for longer. Oral Entocort® has limited effect in UC because more disease is localized in the distal colon. Entocort® enemas may be used in left-sided UC or Crohn's colitis.

The therapeutic therapy of budesonide therapy is not improved with the addition of metronidazole and ciprofloxacin (Steinhart 2002), and the combination of cipro' plus metronidazole is not superior to methyl prednisolone (Prantera 1996).

Table 19. Molecular mechanisms of steroid resistance

- o Abnormalities in absorption/metabolism (liver disease)
- o Altered number of GCS receptors or altered numbers of isoforms (α, β, δ)
- o Altered affinity of GCS for GCS receptors
- o Reduced affinity of the GCS receptor ligands to bind DNA
- o Altered expression of transcription factors (AP-1, NF-k B) and/or cytokines (IL-2, IL-4, p38 activated MAP kinase)
- o Genetic factors (primary steroid resistance, MDR-1 [P-glycoprotein 170], HLA class II allele DRB1*0103)

Adapted from: Farrell RJ, and Kelleher D. *J Endocrinol* 2003; 178(3): 339-46.

Table 20. Common and/or serious adverse effects of the use of glucocorticosteroids

Adverse effect	Frequency
➤ Alopecia	-
➤ Arterial hypertension	+++
➤ Bone marrow suppression	-
➤ Dermatitis	+
➤ Gastrointestinal Toxicity	+
➤ Hirsutism and/or gingival hyperplasia	-
➤ Hyperglycemia and diabetes mellitus	+++
➤ Hyperlipidemia	++
➤ Impaired wound healing	+

Adverse effect	Frequency
➢ Lymphoma or malignancy	-
➢ Myalgia and/or arthralgia	+
➢ Nephrotoxicity	-
➢ Neurotoxicity[a]	+ (psychiatric)
➢ Osteoporosis	+++
➢ Pneumonitis	-

[a]Neurotoxicity includes mainly peripheral neuropathy, headaches, tremor, convulsions, akinetic mutism, and insomnia. ? , Incidence unknown; - not reported; + rarely reported; ++ commonly reported; +++ very frequently reported adverse effect limiting usage of the drug.

Abbreviation: MTOR, mammalian target of rapamycin

Adapted from: Benten D, et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6:1:23-36.

GCS may result in AEs in almost every body system (Table 19), and depending on the dose and duration of use, AEs may occur in half of users. Steroids cause osteoporosis by changing the optimal ratio of Rankl relative to OPG/OCIF. The damaging effect of steroids is greatest in the first 6 months of their use. The ways to reduce the risk of GCS is to use these agents only when absolutely necessary, use steroid-sparing cotherapy (AZA/6-MP, MTX, anti-TNF therapy), use steroids with low systemic bioavailability (Entocort®, budesonide, for acute care of ileocolonic CD). Residronate, a biophosphonate, is approved in the USA to help to reduce the development of steroid –associated osteoporosis (Compston 2003).

Useful Practice Points:

➢ Are you using GCS appropriately?
   o Moderately severe disease
   o Warn about side effects!
   o Caution about short term use only
   o Inform about escape from steroid-dependency and resistance
   o Use locally acting Entocort® for SB/C-CD
   o Dexa scan and bisphosphonates

---

o Antibiotics

Metronidazole is superior to placebo to treat active CD, especially Crohn's colitis. The benefit is small in terms of reducing the CDAI, and not in terms of improving the remission rate (Sutherland et al. 1991). The combination of budesonide, cipro' plus metronidazole is no better than budesonide alone in persons with active CD at any site (Steinhart 2002). Short-term AEs of

metronidazole occur in about half of users, and include a metallic taste in the mouth, gastrointestinal upset, and an antabuse-like reaction when taken with alcohol. The polyneuropathy associated with longterm use of metronidazole is not always reversible. Skin reactions and a mild elevation of hepatic transaminases may occur with ciprofloxacin. More distressing AEs which may occur with cipro', either used by itself or with steroids, includes tendonitis and rupture of the Achilles tendon (Scribano 2008). Metrondiazole increases the effects of statins, sildenafil, calcium channel blockers and the patient's INR.

Probiotics do not have a benefit on the rate of post-operative clinical recurrence, and probably do not improve endoscopic recurrence roles (Prantera et al. 2002, Chermesh et al. 2007).

o Immunosuppressants
- Azathioprine/6-MP
Compared to placebo, azathioprine (AZA) or its active metabolite 6-MP are effective in both inducing (OR, 3.09) or in maintaining (OR, 2.27) remission in CD (Pearson DC 1995). AZA inhibits thiopurine methyl transferase (TPMT) activity (Dewit 2002), thereby increasing the risk of neutropenia, especially in the 11% of the population who carry a heterozygous mutation in the TPMT gene, or the 0.3% who are homozygous (Lennard 1989). The purine analog antimetabolites AZA and its metabolite 6-MP are metabolized further to the active 6-thioguanine (6-TG). 6-TG is incorporated into nuclear RNA, thereby inhibiting the production of DNA in replicating lymphocytes. This in turn reduces lymphocyte proliferation. In addition to impeding lymphocyte proliferation, 6-TG inhibits the inflammatory effect of NK (natural killer) and cytotoxic T-cell function (Novak et al. 2008).

The NNT to achieve remission with AZA/6-MP has been shown by meta-analysis to be 5 (OR 2.36; CI, 1.57-3.53); for steroid sparing effect, the NNT is 3 (OR 3.86; CI, 2.14-6.96) (Sandborn W et al. 2004), and for maintaining remission, the NNT is 7 (Camma et al. 1997). There is no added benefit of combining AZA plus MTX (Soon SY et al. 2004). The relapse rate after stopping AZA is 37% at 1 year, 56% at 2, and 65% at 3 years (Solomon et al. 1993). If AZA maintenance is stopped, the patient will recover the benefit of AZA maintenance if the AZA is restarted.

Mucosal healing achieved with steroids or azathioprine (AZA) does not necessarily lead to lower relapse rates after discontinuation of therapy (Lemann 2002).

Immunosuppressors are being used increasingly and earlier in IBD patients. The AEs of azathioprine (AZA)/ 6-MP are either dose-related or allergic in nature (Table 19). About 5-10% of persons on AZA/6-MP may develop allergic non-dose dependent AEs soon after the medication has been started. These allergic reactions include nausea, abdominal pain, pancreatitis, fever, malaise, skin rash, and anthralgies. Dose-dependent AEs include leucopenia and hepatic toxicity. In persons with IBD who are treated with AZA/6-MP, there is a 4-fold increased relative risk of developing lymphoma (Kandiel 2005); altogether thankfully the absolute risk remains low. In persons with reduced TDMT activity, the enzyme responsible for the conversion of AZA to its active metabolite (6-TG), the risk of myelotoxicity when using the standard rather than a reduced dose of AZA/6-MP is increased 4-fold (Gisbert 2006). In support of measuring AZA metabolites (such as 6-TG), weight based dosing of AZA/6-MP still underestimates the dose 50% of the time (Morales 2007). Allopurinal increases 6-TGN; and ACE inhibitors increase the 6-MP-associated risk of anemia and leucopenia.

- Methotrexate

The therapeutic benefit of methotrexate (MTX) is about 20%, giving a NNT of 5 (Feagan 1995), with a modest efficacy for maintenance of remission (Feagan 2000). MTX must not be used if pregnancy is planned. Regular monitoring of CBC and liver transaminases is essential. The patient on longterm MTX has an increased risk of developing hepatic fibrosis.

When used longterm, methotrexate (MTX) may be associated with the development of hepatic fibrosis or hypersensitivity pneumonitis. MTX is contraindicated in pregnancy because of its teratogenicity. MTX is superior to placebo to induce and maintain remission in CD (Alfadhli 2005).

Table 21. Gastrointestinal complications of immunosuppression

➢ Infection
  o CMV
  o HSV
  o Candida albicans, tropicalis
  o Yersinia enterocolitica
  o *C. difficile*
  o Microsposidia
  o Strongyloides stercoralis
  o *H. pylori*

➢ GI malignancy
  o Lymphomas, including Malt lymphoma
  o Skin cancer
  o Kaposi sarcoma
  o Colorectal cancer
  o Post-transplant lymphoproliferative disorder (PTLD) (EBV)
➢ Cervical dysplasia Diverticular disease, diverticulitis

➢ Perforations (upper or lower GI tract)

➢ Biliary tract
  o Thickened gallbladder wall
  o Sludge
  o Stones
  o Dilated ducts
  o Hydrops

➢ Pancreatitis
  o Acute (CMV, hypercalcemia, alcohol, cholelithiasis, AZA, CyA)

➢ Liver
  o Hepatitis
  o Methotrexate-associated fibrosis

➢ Mucosal injury
  o Diarrhea
  o Ulceration (surgery, NSAIDs; steroids, AZA or MMF-induced slowing of intestinal cell turnover)

Abbreviations: AZA, azathioprine; CyA, cyclosporin A; EBV, Ebstein Barr virus; PTLD, post-transplant lymphoproliferative disorder.

Adapted from: Helderman J, and Goral S. *J Am Soc Nephrol* 2002; 13: page 277-287.

Useful Practice Points:

➢ Immunosuppressants in Crohn's disease
  o Why are you not using an immunosuppressant?
  o Steroid-resistant/-dependent
  o Maintenance therapy

A number of other immunosuppressive agents have been used in patients with CD (Table 21). Methotrexate (MTX) levels are reduced by tetracycline, and increased by penicillin; 5-ASA and NSAIDs; folic acid deficiency worsens MX toxicity.

Table 22. Immunosuppressive agents commonly used in gastroenterology or hepatology, and for each their mode of action, common toxic effects, and recommended monitoring

Agent	Mode of action	Monitoring	Toxic effects
➤ Cyclosporine (CyA), tacrolimus	Calcineurin inhibitor: suppresses IL-2-dependent T cell proliferation	Blood level of CyA, cholesterol, magnesium, Creatinine, BP, BS	Renal, neurologic, hyperlipidemic, hypertension, hirsutism
➤ Prednisone	Other gene transcritption; cytokine inhibitor (IL-1, IL-2, IL-6, TNF, and IFN gamma)	BP, BS, annual eye exam, DEXA scan	(see previous question)
➤ Azathioprine (Imuran®)	Inhibition of T and B cell proliferation by interfering with purine synthesis ($\downarrow$DNA/RNA)	White blood cell count, liver enzymes	Bone marrow suppression, hepatotoxicity
➤ Methotrexate	Folate antimetabolite ($\downarrow$DNA)	Liver biopsy after 1,500 mg (only 2 years maintenance therapy)	Diarrhea, bone marrow suppression
➤ Mycophenolate mofetil (Cellsept®)	Inhibition of T and B cell proliferation by interfering with purine synthesis	White blood cell count	Neutropenia, thrombocytopenia, hyperlipidemia

Useful Practice Point:
- ➤ Antibiotics in Crohn's Disease
  - o Best evidence for MTZ, not Cipro' or Cipro + MTZ
  - o Metallic taste
  - o Peripheral neuropathy
  - o Antabuse-like reaction
  - o May be treating bacterial overgrowth
  - o Warn about AAD or C.difficile development

Agent	Mode of action	Monitoring	Toxic effects
➢ Sirolimus (Rapamycin)	Inhibition of TORC, which disrupts IL-2 induced intracellular signalling in lymphocyte	Blood level	Cytokine release syndrome, pulmonary edema, increased risk of infections
➢ OKT3	Blocking of T cell CD3 receptor, depletion of effector T cells and T regs, preventing stimulation by antigen	$CD3^+$ count	Hypersensitivity reactions with basiliximab
➢ IL-2 receptor blocker	Competitive inhibition of IL-2 receptor on activated lymphocytes	None	

Abbreviations: BP, blood pressure; BS, blood sugar; DEXA, DEXA scan for bone mineral density; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.
Adapted from: Martin P, and Rosen HR. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 2049.

➢ Anti-TNF therapy

In the patient with active inflammatory CD who has failed an adequate course of standard therapy with GCS and immunosuppressants, anti-TNF therapy is an option. Relative contraindications (Table 20) must be carefully considered before initiating this therapy and adverse effects (Table 21). The major AEs of infections and lymphoma may be the result of the use of the combination of an anti-TNF, AZA/6-MP and GCS (Lichtenstein 2006). IFX is considered to be useful for hospitalized UC patients with severe or moderately severe UC (Jarnerot 2005). There have been no reports of hepatospheric T-cell lymphoma in IBD patients on monotherapy with anti-TNF therapy, or a combination of influximab or adalimumab with methotrexate. If anti-TNF therapy is added to AZA or MTX because of failure to respond to these immunosuppressants, then it would appear to be reasonable to stop immunosuppressant once the anti-TNF therapy has been started, especially since withdrawal of aziothioprine and continuation of the infliximab (IFX) alone has no effect on the continued response to IFX, as compared to patients on both IFX and AZA (Van Assche 2008.). For patients with secondary loss of response to IFX, switching to ADA gives "recapture" remission rates of 21% at 4 weeks and 40% at one year; switching from IFX to certolizumab pegol at 6 weeks gives a "recapture" response of 60% and remission of 40% (Rutgeerts 2008).

The two large international placebo-controlled randomized clinical trials in CD (RCTs) support the results of earlier smaller studies of clinical response and maintenance of remission in CD when using the anti-TNF biological agent, infliximab (IFX) (Kohn 2008). There are many further studies of infliximab as well as adalimumab and certolizumab in CD. Note that from many studies using TNF blockers (TNFB) such as infliximab (IFX), adalimumab (ADA), or certolizumab (CER) exclude those CD patients who were non-responsive to induction therapy.

Table 23. Relative contraindications to anti-TNF therapy

- o Allergy to anti-TNF
- o Intestinal stenosis
- o Fistulizing disease with abscess
- o Fistulae to bladder
- o Untreated active infection (TB, HBV, HCV)
- o Multiple sclerosis, optic neuritis
- o Congestive cardiac failure (grade III, IV)
- o Lymphoma
- o Pregnancy
- o Acute liver failure

Abbreviations: HBV, hepatitis B viral infection; HCV, hepatitis C viral infection; MS, multiple sclerosis; TB, tuberculosis; CyA, cyclosporin; BP, blood pressure; BS, blood sugar; WBC, white blood cell count

When determining the NNT, the therapeutic gain must be recognized, eg IFX response minus placebo response. For example, in the Act 1 and 2 studies, the rate of clinical remission fell over time, the proportion of patients in remission was only about half, and the TG over time was only about 20% (Figure 4). Thus, while anti-TNF has changed the way in which some physicians change the way CD is treated, and while some patients do very well, in fact the therapeutic gains are small, these rates may become higher once the reason for the development of primary and secondary treatment failure has been overcome (Table 22).
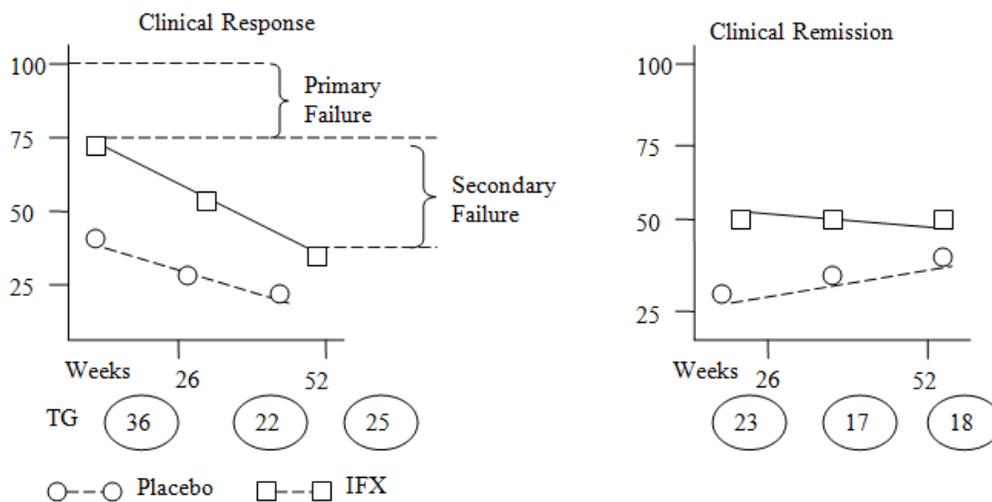
Abbreviation: TG, therapeutic gain (clinical response/ remission with IFX minus placebo

Figure 4. The Act 1 and 2 Randomized clinical trials of Infliximab for induction and maintenence of remission in patients with active Crohn disease.

Mucosal healing prolongs the time to relapse with IFX (D'Haens, et al. 2002). When relapse occurs, "it is striking that upon relapse, endoscopy shows an identical pattern of lesions and of locations of disease as observed prior to healing under biologic treatment" (Rutgeerts et al. 2008). Note that there may be drug-drug interactions with agents used in therapy of CD (Table 24).

Table 24. A definition for primary and secondary infliximab failures in patients with inflammatory bowel disease (IBD) and their proposed mechanisms

➢ Primary – lack of response due to high pre-treatment TNF-α levels, or TNF-α independent inflammatory pathways

➢ Secondary – loss of initial symptomatic response to anti-TNF
- o Mechanisms
  - – Antibody to TNF
  - – Increased clearance of TNF
  - – Non-TNFα dependent
  - – Development of IBD-related complications e.g. stricture, abscess
  - – Non-IBD related symptoms (e.g IBS)
- o Anti-I (inliximab) antibodies, (e.g., use of on demand infusions):
- o Rapid infliximab metabolism
- o Low trough infliximab levels

Abbreviation: IBD, inflammatory bowel disease; IBS, irritable bowel syndrome

Table 25. Useful background summary pointers of IBD drug interactions

- o 5-ASA increases INR, 6-TGN and methotrexate, and decreases digitalis levels
- o Allopurinal increases 6-TGN
- o ACE inhibitors increase the 6-MP-associated risk of anemia, leucopenia
- o Methotrexate (MTX) levels are reduced by tetracycline, and increased by penicillin; 5-ASA and NSAIDs; folic acid deficiency worsens MX toxicity
- o Metronidazole increases the effect of statins, sildenafil, calcium channel blockers and ↑ INR
- o Steroids cause osteoporosis by changing the optimal ratio of Rankl relative to OPG/ OCIF. The damaging effect of steroids is greatest in the first 6 months of their use
- o Anti-TNF therapy causes 6.4 fold increase in mortality rate in persons with pre-existing pulmonary disease (256-97)

Abbreviations: MTX, methotrexate; OCIF, osteoclasto genesis inhibitory factor; OPG, osteoprotegerin

Useful Practice Points:

➢ Is there a good reason to use experimental biological therapy?
- o Failed standard step-up medical therapy: 5-ASA→GCS→AZA/MTX
- o Willing, informed patient, with good cost coverage for Rx

o **Maintenance of remission**

Steroids provide no benefit to prevent relapse of CD (Sims and Steinhart 2001, Steinhart 2003). Budenoside prolongs the time to achieve a CD recurrence at 1 year (Hellers 1999), but should not be used for longer. Thus, steroids should be used for maintenance therapy in CD (or UC). The locally acting steroid Entocort® may be used in mild or moderately active ileal or ileocolonic CD, but must not be used in UC, because it is ineffective for flares, and is also ineffective for maintenance. If the patient is steroid-refractory (failure to enter remission despite high-dose and IV GCS) or steroid-dependent (remission obtained with GCS, but either a reflare as the GCS dose is tapered, or a reflare within 3 months stopping the GCS), the patient should be started an either immunosuppressive therapy (AZA/6-MP, MTX) or anti-TNF therapy; colectomy also remains a viable option.

There is superior IFX response in persons who have already been on, or who are concurrently on AZA (Hanauer 2002, Su 2005) or MTX (Alfadhli 2005). This benefit is in terms of greater initial clinical efficacy, less secondary loss of response, and less overall toxicity including less development of antibodies to infliximab (ATI). Longer duration of remission with IFX plus AZA has been shown in children with CD (Cottone 2000). Giving a bolus of steroid plus histamine is useful to prevent the redevelopment of infusion reactions to infliximab (secondary prophylaxis), but has no role as primary prophylaxis (given as a routine to prevent the first infusion reaction) (Forbes 2008).

➢ **Comparison of therapies in CD and UC**

There are differences as well as some similarities in the therapy for induction and maintenance of remission of CD and UC (Table 25). SASP and 5-ASAs are much better for treatment of mild/mild-moderate UC than CD, and are also much better for maintenance of remission in UC than CD. Entocort® has no role for induction of remission in UC, or for maintenance of remission in either CD or UC. There is only limited data supporting TNFβs as rescue induction therapy for steroid failures in severe UC, or as maintenance therapy.

Table 26. Comparison of Therapies of CD and UC

	CD		UC	
	Induction	Maintenance	Induction	Maintenance
➢ Sulfazalazine (SASP)			+	+
➢ Mesalamine(5-ASA)	+	+/-	+	+
➢ Metronidazole / Cipro	+ (colitis)	+ post-resection	-	-
➢ Glucocorticosteroids (GCS) prednisone	+	no	+	
➢ Budesonide	ileocolonic	Up to 12 months	-	-
➢ Azathioprine (AZA), 6-MP	+	+	+	+
➢ Methotrexate (MTX)	+	Post-resection	-	-
Cyclosporin (CgA)	-	-	+	-
➢ TNFB				
Infliximab (IFX)	+	+	+	+
Adalimumab (ADA)	+	+		
Certolizumab	+	+		

Abbreviations: TNFB, TNF blockers, anti-TNF drugs

(Adapted from Schreiber 2007, Pearson 1995, Alfadhli 2005, Hanauer 2002, Sutherland 2003, Shibolet 2005, McDonald 2005).

> **Pregnancy**

The effect of IBD on pregnancy and of pregnancy on IBD will not be considered here. When CD becomes active during pregnancy, the disease is treated as if the CD patient were not pregnant, except that the use of methotrexate or thalidomide is prohibited (Table 27). A summary of useful background, pointers about IBD and pregnancy is made in Table 28. It is important to be aware of the interactions between IBD-treating medications and other drugs, and the effect of non-IBD treating drugs on the efficacy of medications used to treat IBD (Table 24). Colectomy and ileoanal anastonesis increases infertility 3-fold (Waljee 2006) and the incidence of abnormal PAP smears is increased in women with IBD (Kane 2008).

Table 27. FDA category for pregnancy, and recommendations for breast feeding of medications used in patients with IBD

Drug	FDA category	Recommendations for breast feeding
➢ Balsalazide	B	Yes
➢ Mesalamine	B	Yes
➢ Sulfasalazine	B	Yes
➢ Olsalazine	C	LHD
➢ Rifaximin	C	LHD
➢ Amoxicillin/clavulinic acid	B	Probably compatible
➢ Metronidazole	B	No
➢ Ciprofloxacin	C	LHD
➢ Corticosteroids	C	Yes
➢ Cyclosporin	C	No
➢ Tacrolimus	C	LHD
➢ **Thalidomide**	**X**	**No**
➢ AZA/6-MP	D	LHD
➢ **Methotrexate**	**X**	**No**
➢ Adalimumab	B	LHD
➢ Infliximab	B	LHD
➢ Loperamide	B	Yes
➢ Diphenoxylate	C	No

Abbreviations: LHD, limited human data

Printed with permission: Kane SV. *2008 ACG Annual Postgraduate course book*: page 27.

First Principles of Gastroenterology and Hepatology   A. B. R. Thomson and E. A. Shaffer

Table 28. Summary pointers of IBD and pregnancy

➢ Colectomy and ileoanal anastonesis increases infertility 3-fold (Waljee 2006.)

➢ The incidence of abnormal PAP smears is increased in women with IBD (Kane 2008).

While earlier studies have suggested poor outcome of pregnancy in IBD patients with active disease (Miller 1986), this has not been confirmed more recently (Mahadevan 2007). In a community based study from northern California, the activity of IBD at conception usually carries through the pregnancy as well as post-partum period (Young 2009). Although the only contraindications to vaginal delivery in Crohn disease is active perianal disease, the likelihood of having a Caesarean section is increased 1.5 times above that of non-IBD women (Cornish 2007). Having an extensive episotomy at delivery may contribute to the 18% risk of a woman developing perianal diseas after childbirth (Iinyckyj 1999). Breastfeeding may or may not be a risk factor for the development of Crohn disease in the infant (Klememt 2004; Jantchou P, 2005). Flexible sigmoidoscopy during pregnancy does not increase the risk of premature labout (Cappell 1996). Only 29-44% of IBD patients breastfeed their infant (compared to an American standard of 60%), and 43% of those mothers who breastfeed their babies flared, possibly because 74% of those who flared had stopped maintenenace medications (Kane 2005).

o **Management of Perianal CD**

There are several methods used to classify fistulae. Likewise, there are several diagnostic tests that may be useful to diagnose the presence of fistulae in CD, and the anatomical position (Table 28) (Schwartz 2001).

Table 29. Different schemes for the classification of any type of gastrointestinal fistulae, based on anatomy, output volume, and etiology

Scheme	Classification
➢ Anatomical	➢ Internal, external − Low, high ➢ Simple, complex
➢ Relationship to dentate line: high (above) or low (below)	
➢ Relationship to the anal sphincters	o Inter-sphincteric o Trans-sphinteric o Supra-sphincteric o Extra-sphincteric
➢ Simple	o low, single external opening, no pain or fluctuation, no rectovaginal fistula (RV) or anorectal stricture
➢ Complex	o high, multiple external openings, pain or fluctuation, RV fistula or anorectal stricture, active rectal inflammation.

Scheme	Classification

➤ Output volume	➤ Pancreatic
	  − Low (<200 ml/day)
	  − High (≥200 ml/day)
	
	➤ Intestinal
	  − Low (<500 ml/day)
	  − High (≥500 ml/day)

➤ Etiological	➤ Underlying disease

Printed with permission: Messmann H, et al. *Best Practice & Research Clinical Gastroenterology* 2004, page 811.

There are open-label studies but no randomized, controlled trials (RCTs) of the use of ciprofloxacin (cipro'), metronidazole, or cipro' plus metronidazole in perianal disease (Siemanowski and Regueiro 2008), and no studies of maintenance therapy. Antibiotics may be a useful "bridge" to the use of immunomodulators (Dejaco 2003). Studies where the secondary endpoint was fistula healing show benefit of AZA/6-MP (Pearson et al. 1995). There is limited evidence for a possible benefit of low-dose tacrolimus (0.05 mg/kg over 12 hours) (Gonzalez-Lama 2005).

The treatment of perianal CD has been revolutionized with the introduction of anti-TNF therapy (Siemanowski B and Regueiro M 2008). Anti-TNF is effective in closing (Present 1999) and maintaining closure (Sands 2004) of perianal fistula when therapy (IFX, 5mg/kg) every 8 weeks.

Table 30. Treatments for perianal CD

➤ Medical	➤ Surgical
o Drugs used to treat Crohn disease o CO_2 laser ablation o Hyperbaric O_2 o Injection of silver microspheres with antibiotic	o Seton surgical placement o Glue o Fistulotomy o Endorectal advancement flap o Fecal diversion o Proctocolectomy o Fistulectomy

Abbreviations: CD, Crohn disease; DRE, digital rectal examination; EUA, examination under general anaesthesia; EUS, endoscopic ultrasound; PF, perianal fistulae
* Patients who have a single fistula and no rectal inflammation on endoscopic examination will often respond to a fistulectomy.

In the Accent II study, those CD patients with perianal fistulas who were initial responders to IFX (≥50% reduction in draining fistulas), by week 54 of treatment, 36% of those on IFX and only 19% of those on placebo had a complete cessation of drainage of all their fistulas, even though most of the patients did not achieve complete closure of their fistulas over the course of one year (Baert 2003). This reflects the fact that fistulas may remain active long after they stop draining (Schwartz 2005). Complete healing may be accessed by EUS or MRI. In the CHARM study (Colombel 2007), again as a secondary outcome measure, at 56 weeks 33% of these treated with adalimumab (ADA) versus 13% of these given placebo had closure of their fistula. Patients may enjoy a better fistula closure rate and a more durable response to IFX if they have an examination under anaesthesia and seton placement prior to medical therapy (Regueiro 2003).

8. Surgery

Up to 80% of CD patients will require IBD-related surgery during the lifetime of their illness. There are the usual indicators for surgery in CD such as obstruction and proliferation, as well as failure of medical therapy, perianal sepsis, drainage of abscesses, as well as perianal, enterocutaneous, enterovaginal or enterovascular fistulas. A side-to-side rather than an end-to-end anastomesis results in fever complications but no difference in recurrence rates (Smillis 2007).

In the first year after surgery, symptoms will develop in 20-30%, and for every year thereafter 10% will develop symptoms. Curiously, there is a disconnect between post-operative symptoms and recurrent inflammation: 70% of post-surgery CD patients develop endoscopic lesions in the first year after surgery, usually in the preanastomatic ileum, in bowel that was both macroscopedly and microscopedly normal prior to surgery, and yet only about a third of these persons with post-operative recurrent CD will have symptoms (Rutgeerts 1990, Rutgeerts 1991) (Table 30).

Table 31. Two Year Recurrence Rates after Surgery for CD

	PL	5-ASA	6-MP
➢ Clinical recurrence rate	77%	58%	50%
➢ Endoscopic recurrence rate	64%	63%	43%

Abbreviations: PL; placebo (Hanauer 2004)

For CD structures less than 5 cm in length, endoscopic dilation may give immediate success rates of 71%-100% (Van Assche 2008), with 0%-11% having a complication of proliferation or bleeding. The symptomatic recurrence is 13-100% after an initially successful balloon dilation. Repeat dilation is appropriate, "…but the length of the symptom-free internal will be the main parameter used to decide between surgery and re-do endoscopic balloon dilation" (Van Assche et al. 2008). Endoscopic stenting may reduce the recurrence rates after endoscopic balloon dilation (Matsuhashi 2000), but the injection of steroids into the affected area may actually accelerate relapse (East 2007).

Table 32. Sub-acute small bowel obstruction in CD

Causes	Diagnostic procedures*	Management
➢ Active inflammatory CD	o Plain abdominal films	− Treatment of inflammatory CD (avoid anti-TNF)
➢ Adhesions, bands	o Conventional CT	
➢ Stricture	o CT enterography	− Through-the-scope balloon dilation
➢ Fruit pits	o Small bowel (gastrograffin) x-ray	
➢ Gallstone ileus		− Adjuvent steroid injection into narrowing
➢ Enterolith	o Abdominal ultrasound	
➢ Endometriosis	o Doppler ultrasound	− Expandable metal stents
	o MR enterography	− Stricturoplasty
	o FDG-PGT (18F-flurodeoxyglucose positron emission tomography [PET])	− Open or laparoscopic surgical resection

Fibrostomatic disease has a more indolent course, whereas persons with abscesses or fistulas as the indication for the initial surgery tend to have the same type of aggressive disease when it recurs post-operatively. Sub-acute small bowel obstruction is common in CD, and when this occurs in the setting of previous surgery for CD, the physician must distinguish between surgery-associated bonds and adhesions, versus the development of active inflammatory CD, versus a CD-related stricture (Table 31). The usual diagnostic procedures may be considered. In addition to the usual management of the patient, the obstruction and the CD, there are a number of CD-associated therapies which may be considered.

*the use of capsule endoscopy is contraindicated because of the possibility of a stricture, which would potentially lead to the need for surgery to remove the capsule.

Abbreviations: CD, Crohn disease; PET, positron emission tomography; SBO, small bowel obstruction

9. Nutrition and CD
   o Nutritional Deficiencies

There is a high prevalence of nutritional deficiencies in IBD, especially in CD (Table 32) (Lochs 2009). The origins of malnutrition in CD are multifactorial (Table 36) but dietary restrictions (due to intolerance of diet or therapeutic fasting) are the most important.

Table 33. Frequency of Nutritional deficiencies in IBD

Nutritional deficiencies	CD (%)	UC (%)	Nutritional deficiencies	CD (%)	UC (%)
➢ Weight loss	65–75	18–62	➢ Potassium	6–20	+
➢ Hypoalbuminaemia	25–80	25–50	➢ Vitamin A	11	Not reported
➢ Intestinal protein loss	75	+	➢ Vitamin B_1	+	Not reported
➢ Negative nitrogen balance	69	+	➢ Vitamin C	+	Not reported
➢ Anaemia	60–80	66	➢ Vitamin D	75	+
➢ Iron deficiency	39	81	➢ Vitamin K	+	Not reported
➢ Vitamin B_{12} deficiency	48	5	➢ Zinc	+	+
➢ Folic acid deficiency	54	36	➢ Cu	+	+
➢ Calcium	13	+	➢ Metabolic bone disease	+	+
➢ Magnesium	14–33	+			

Table 34. Causes of malnutrition in IBD

o Decrease in oral intake	o Restrictive diets o Therapeutic fasting o The disease itself: diarrhea, abdominal pain, nausea and vomiting, etc o Alteration in taste: due to drugs, vitamin and mineral deficiencies, pro- inflammatory mediators o Anorexigenous effect of pro-inflammatory cytokines
o Gastrointestinal losses	o Diarrhea o Rectorrhagia/hematochezia o Loss of mucus and electrolytes o Protein-losing enteropathy
o Metabolic disorders	o Increase in resting energy expenditure o Enhanced fat oxidation

o Increase in nutritional requirements	o Inflammatory states o Increased basal oxidative metabolism o Infectious complications o Post-surgery
o Drug interaction	o Glucocorticsteroids and calcium reabsorption o Corticoids and protein catabolism o Salazopyrine and folate malapsorption o Methotrexate and folate deficiency o Cholestyramine and liposoluble vitamin malabsorption o Antimicrobials and vitamin K o Anti-secretors (PPI_0, N_2-RAs) and iron malabsorption
➢ Poor absorption of nutrients	o Reduction of the absorptive surface: intestinal resection, enteric fistulas o hypertrophy of the villi with increased immature enterocytes o Blind loops, bacterial overgrowth o Poor absorption of bile salts wth ileal inflammation or resection

(Lucendo 2009)

Abbreviations: PPIs, proton pump inhibitors; H_2-RAs, H_2 receptor atagonists

Also included are: the increase in energy requirements, the malabsorption of nutrients in the case of extensive intestinal involvement, gastrointestinal losses and the interaction between nutrients and drugs (Lucendo 2009). Furthermore, the underlying inflammatory mediators of the physiopathology of IBD (Cabré 2001), such as tumor necrosis factor (TNF)-α, and interleukins-1 and -6 can increase catabolism and lead to anorexia.

In quiescent, IBD energy and substrate metabolism is normal, or shows the typical changes of a shortage of energy intake with a decrease in carbohydrate and an increase in fat oxidation. During the active phase, patients develop a mixed picture of an inflammatory reaction and malnutrition, with slight increases in energy expenditure and a relative increase in fat and decrease in carbohydrate oxidation. These changes are non-specific and are quickly reversible when patients are given nutritional support.

Enteral nutrition may be of benefit as primary therapy in children with CD, even to the point of being steroid-sparring and improving the child's growth and development. It is unknown what is mechanism of the benefit of enteral nutrition in CD beyond the nutritional benefit itself (Table 34). It is also now known why enteral nutrition fails as primary therapy in adults with CD. The value and benefits deriving from the use are of enteral nutrition directly dependent on the geographical location of the disease, its extent and severity and Enteral feeding is therefore especially indicated for CD patients when the small intestine is affected, while there is no evidence which supports the use of enteral nutrition in the treatment of UC except for the correction of nutrient deficiencies (Lucendo 2009). Intestinal rest is not beneficial to control IBD (Greenberg et al. 1988).

Apart from the intake of calories, proteins and micronutrients, enteral nutrition using liquid formulas has therapeutic function, especially in children with CD (Heuschkel 2004) (Table 34). This therapeutic effect is independent from the nitrogen source used (Goh 2003). The fat composition of the enteral diet seems to be important in terms of its therapeutic effect (Gonzalez-Huix et al. 1993), as this fat composition could be the key factor of the diet's therapeutic action on the disease (Gassull 2002). The n-3 PUFAs (polyunsaturated fatty acids) may be prove effective for maintaining CD in remission, although more extensive studies are required in order to unequivocally establish the utility of these therapies (Lucendo 2009).

Table 35. The possible mechanisms of the beneficial effect of enteral nutrition in CD

- ➢ Improvement of nutritional status
- ➢ Down regulation of pro-inflammatory cytokines
- ➢ Anti-inflammatory effects
- ➢ Promote epithelial healing
- ➢ Decrease gut permeability
- ➢ Decrease antigenic load to the gut, bowel rest
- ➢ Modification of gut flora

(Hartman 2009)

Probiotics are "live micro-organisms which, when consumed in adequate quantities, confer a health benefit on the host" (Shanahan 2004). Prebiotics are "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one, or a limited number of bacteria in the colon, thus improving host health" (Bengmark 2005, Lim 2005). The rationale behind prebiotic use is to increase the endogenous numbers of beneficial bacterial strains including lactobacillus and bifidobacterium. Another viable option is to use both prebiotic and probiotic administration in conjunction, referred to as synbiotics (Bengmark 2005, Bengmark 2005). The rationale behind synbiotic treatment is that the combined probiotic and prebiotic would exert a beneficial effect greater than would be observed when administered individually.

Probiotics may function via the modulation of cell proliferation and apoptosis (Ichikawa 1999). Probiotics have the potential to be beneficial in the treatment of IBD due to their capacity to prevent the colonisation of pathogenic bacteria, reduce inflammatory cytokine expression, enhance epithelial cell proliferation, inhibit apoptosis and provide metabolic energy for enterocytes (Geier et al. 2007) It may also be the case that our genetic profile may predispose our responsiveness to probiotic treatment, as is the case with chemotherapy (Kaneta 2002; Kihara 2001). Identification of these "probiotic responsiveness genes" may lead to screening to determine i) whether a patient will be responsive to probiotic therapy, and ii) to which probiotics they would respond more efficiently (Geier 2007).

There is no reliable reproducible evidence to support the use of probiotics in the induction or maintenance of remission of CD. The mode of action of probiotics is not completely understood. There have been a large number of probiotic species identified, most of which have differing mechanisms of action. Further complexity stems from the finding that the mode of

action of a given probiotic can differ based on the presence of other probiotics or enteric bacteria in the surrounding environment, and also the disease setting in which the probiotic is used (Shanahan 2004).

10. Colon Cancer Surveillance

From the data in UC, it is assumed that the same principles for surveillance for colorectal cancer (CRC) apply in the person with left-sided Crohn's colitis (CC) or CC plus PSC. For further details on this topic in UC, please see the chapter on UC. There is an increased risk of CRC in UC (Chambers 2005, Eaden 2001) (Table 35, Figure 5).

Table 36. Risk of CRC in UC over time

Duration of UC, years	Pancolitis, %	All patient risk, %
10	5	2
20	20	8
25	40	-
30		18

*Includes localized left-sided disease as well as pancolitis

The standardized incidence ratio (SIR) for CRC to develop in UC is above 3, and for Crohn's colitis (when over one third of the colon is affected), SIR for CRC is 2 (Lashner 2008). In UC patients, the first "screening" colonoscopy should be done after 8-10 years of pancolitis, or after 15 years of left-sided colitis (Chambers 2005) (Table 34). If there is only proctitis, then no special screening is necessary beyond the guidelines for the "average risk" individual. If primary sclerosing cholangitis (PSC) is diagnosed in the patient with UC, screening colonoscopy should be done immediately at the time of PSC diagnosis, and then with annual surveillance colonoscopies thereafter (Itzkowitz 2005).

There are numerous guidelines for colorectal cancer screening in the person with pan UC (Table 36), and these principles are often applied to CC.
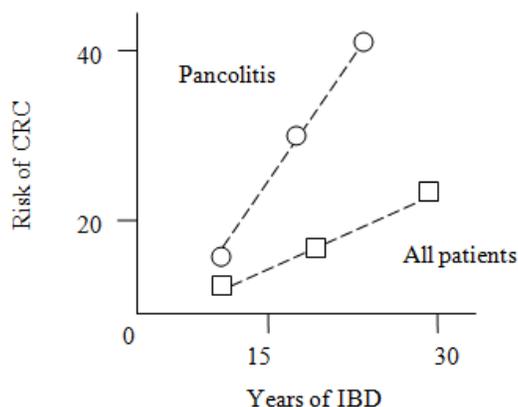
Figure 5. Risk of developing colorectal cancer (CRC) in persons with UC

Table 36. Guidelines for colonoscopic surveillance of UC patients for dysplasia/CRC

Years of UC	British Guidelines[1]	American Guidelines[2]
10 ⎫ ⎬ 19 ⎭	q3yr	Coloscopy every 1-2 years
20 ⎫ ⎬ 29 ⎭	q2yr	Colonoscopy after every 1-3 years after 2 negative examinations, until the disease has been present for 20 years
30 ⎫ ⎬ 40 ⎭	q1yr	Colonoscopy every 1-2 years

(Cornell 2008); [1] (Eaden 2002, Mpofu 2004); [2](Kornbluth 2004, Itzkowitz 2005)

A simplification of the this approach would be to perform a colonoscopy every 1-2 years after the initial screening in all UC/CC patients. CRC surveillance in UC increases live expectancy by 1.2 years (Provenzale 1995), with cost-effectiveness similar to other accepted medical practices such as Pap smear testing (Provenzale 1998).

At the time of screeing colonoscopy for CRC, the colonoscopist takes multiple untargeted random mucosal biopsies are taken from 4 quadrants every 10 cm of bowel, at intervals suggested by various guidelines. In the hands of expert pathologist, the risk of false-positive and false-negative diagnosis of dysplasia is 5% and 48%, respectively (Provenzale 2001).

A number of methods have been introduced to improve the diagnostic sensitivity and specificity of detecting dysplasia or colorectal cancer, including improved training of endoscopist and improved equipment, and as well as new laboratory procedures (Table 38). While such a surveillance program for UC and Crohn`s colitis is the community standard of care in Canada, there is no evidence that it saves lives or is cost-effective. The likelihood of finding dyplastic lesions in UC and CC may be increased as compared with white light colonoscopy (WLC) by using targeted biopsies in conjunction with new endoscopic imaging modalities (Kiesslich 2008). These include chromoendoscopy, narrow band imaging, optical coherence tomography, confocal laser endomicroscopy, and CT colography.

Table 37. Proposed methods to Improve Colonoscopic Surveillance for Dysplasia and Colorectal Cancer

➢Improved Endoscopist	o Heightened intensity and strictness of training, with certification of competence o Regular introduction and maintenance of quality control methods o Improved bowel preparation o Improved patient sedation identification of cecal landmarks o Slow withdrawal of scope
➢Improved Equipment	o Chromoendoscopy o Narrow band imaging (NBI) o Coherence tomography o Confocal laser endomicroscopy o CT colography
➢Laboratory Testing	o p53, β-catenin, p16

Chromoendoscopy (intravital staining, contrast endoscopy) permits assessment of the pit patterns (Jung 1999). Chromoendoscopy, as compared with conventional WLC and random biopsies, increases the diagnostic yield of intraepithelial neoplasia by 3- to 4.5-fold. Chromoendoscopy is included in USA guidelines for surveillance in patients with longstanding UC (Itzkowitz 2005).

Narrow band imaging (NBI) illuminates the tissue surface, and allows optimal visualization of the microvascular structure of the mucosal layer (Gono 2004). Both chromoendoscopy and NBI increase the sensitivity by 17% and the specificity by 31% of the differentiation of neoplastic from non-neoplastic lesions in UC.

Optical Coherence Tomography (OCT), based on optimal interferometry, provides real-time high-resolution images formed by detecting light that is reflected back from the mucosal subsurface tissue microstructure. The diagnostic sensitivity and specificity to detect transmural inflammation is 70% and 83%, respectively (Shen 2004). Clearly, WLC is inferior to chromoendoscopy, NBI and OCT for the detection of early neoplasia.

In confocal laser endomicroscopy, a confocal laser microscope is incorporated into the distal top of a conventional video endoscopy (WLC), allowing subsurface analysis of the intestinal mucosa and *in vivo* histology. A fluorescent contrast agent is applied. High contrast images are obtained from the confocal endomicroscope, as well as simultaneously obtaining standard endoscopic standard images. Surface and subsurface analysis is obtained, with an accuracy of 99% (sensitivity, 97%; specificity, 99%) to detect the presence of neoplastic changes (Kiesslich 2007).

CTC (CT colonoscopy) is now approved in the USA for use in CRC screening in non-IBD patients. Strictures, pseudopolypos and fistulae can be seen in IBD (Carrascosa 2007, Andersen 2006). The use of CTC for CRC screening/surveillance in Crohn colitis or UC has not been validated.

The drawback to WLC is that the dysplastic lesions which may develop in UC may be flat and not detectable, or elevated yet small and thus not readily detectable. These Endoscopcially detectable and elevated lesions have been called DALMs (dysplasia-associated lesion or mass) (Blackstone 1981). On the basis of the gross appearance of these lesions, DALMs are further classified as adenoma-like or non-adenoma-like (Odze 1999).

Similar to sporadic adenoma, the adenoma-like DALMs which occur in UC are "well-circumscribed, smooth or papillary, non-necrotic, sessile or pedunculated polyps, that are usually easily removed by routine endoscopic methods…" (Odze 2008). The non-adenoma-like lesions include "velvety patches, plaques, irregular bumps, and nodules, wart-like thickenings, structuring lesions, and broad-based masses…not typically amenable to be removed by colonoscopy".

The adenoma-like DALMs have a low probability of associated malignancy (Rutter 2004), and so can be managed by endoscopic polypectomy plus continued colonoscopic surveillance. In marked contrast, the non-adenoma-like DALMs have a 36-85% risk of either synchronous or metachronous cancer (Odze 1999, Bernstein 1994).

If the adenoma-like DALMs occur proximal to the area of colitis (at least with the example of UC), they are managed as if they were unrelated to the UC, ie as if they were sporadic adenomas, with endoscopic removal followed by regular colonoscopic surveillance (Odze 2004). In marked contrast, the adenoma-like DALMs which occur in an area of colitis (eg,

UC-associated dysplastic lesion rather than a sporadic adenoma) must be considered as having a high malignant potential, and total colectomy is required (Friedman 2003).

About half of these UC patients who have had a sporadic adenoma removed by colonoscopy will have a recurrence of an adenoma, again requiring polypectomy and further follow-up (Friedman 2003, Odze 2004). The approach of polypectomy and colonscopic follow-up is the standard of care, as long as the adenoma has been completely removed, the margins are free of dysplasia, and there is no flat dysplasia anywhere in the colon either close to or away from the polyp.

Immunohistochemical changes (such as p53, B-catenin, APC, p16) have too low a sensitivity and specificity to be used to help distinguish between the sporadic and the colitis-associated adenomas which occur in the patient with UC (Odze 2000).

11. Practical Steps in IBD Care

Preveting Common Errors in the care of Ptients with IBD: Ask yourself a few questions

- o Is the diagnosis of IBD correct?
- o Are you prescribing the right 5-ASA preparation?
- o Are you using GCS appropriate?
- o Should an immunosuppressant be used?
- o Why are you not using an immunosuppressant?
- o Is there a good reason to use biological therapy?

What does the Primary Care Physician (PCP) Need to/Want to know about IBD?

- o Typical patient presentation & profile
- o Major differential
- o PCP-based nvestigations
- o First line therapy for new IBD
- o Identify and treat a recurrence
- o When to refer

About IBD?

- o Number of patients   300/105
- o Number of PCPs   1/103
- o Every PCP will have 2 to 3 IBD patients
- o Number of PCP/GI in Canada   35,000 vs 500

How does the Patient Walk into Your Office?

- Diarrhea, pain, malaise, pallor
- Alarm symptoms: blood, nocturnal symptoms, fever, weight loss
- Extraintestinal symptoms: mouth, joints, skin, liver, kidney
- Perianal disease

Have you considered Organic Cuases of Chronic Diarrhea?

- Stomach – ZES, Rx, resection
- Hepatobiliary – Jaundice, pruritus (cholestasis)
- Pancreatic – alcohol, trauma, cystic fibrosis
- SB-LV, "F's" foul, flush, fat, food, flatus
- LB-SV, tenesmus, incontinence

Abbreviations: SB, small bowel; LB, large bowel; SV, small volume; LV, large volume

---

Do I need a Second Opinion for the IBD/IBS-D Patient?

- Celiac disease – antitransglutaminase
- Bacterial overgrowth – H2 breath test with lactulose
- Bie salt wastage – 72 hour stoll collection
- Microscopic colitis – rectal biopsy

Abbreviations: IBS-D, diarrhea-predominant irritable bowel syndrome

---

If IBD is suspected. If you "imagine", Then "Image"

- Ulcerative Colitis (UC) $100/10^5$
- Crohn's Disease $200/10^5$
  - Ileum 40%
  - II + C 40%
  - Colon 20%
- Image
  - ACBE $\pm$ sigmoidoscopy/colonscopy
  - Small bowel (FT, enteroclysis, CT, MRI)

Why distinguish between UC and CD?

➢ Acute-targetd 5-ASA; CYS; surgery
➢ Maintenance 5-ASA for UC, AZA for CD
➢ Steroid resistance AZA for UC/CD TNFβ
➢ Nutritional complications
➢ CRC surveillance (CD-C involvement)
➢ Type/time of surgery

First Line therapy for IBD

➢ Diagnosis
➢ Information
➢ Complications
  o N utrition
  o O steoporosis
  o P sychological
  o 5-ASAs

5-ASAs for IBD

➢ Mesalamine
  o Plus sulfa
  o Plus coating
➢ Release pattern
  o PO
    − TI
    − C
  o PR
➢ SB + C Pentasa
  o Salofalk
  o Asacol (400 mg)
  o Enemas (4 g), suppositories (500 mg)

Are you prescribing the right 5-ASA preparation?

➢ Mesalamine vs Salazopyrine – cost, AEs

➢ PO – dose, target site

➢ Local – enemas, suppositories $\pm$ PO

Are you Choosing the correct 5-ASA product?

- Adverse effect
  - SASP 30%
  - Mesalamine 1 to 5%
- Dosing
  - QID – TID – TID once a day!
- Route
- Cost
- Theoretical Differences

Use of Mesalamine in IBD

- Acute 4 g P.O., P.R.
  - Caution: slow onset, long duration
- Maintenance 2 g
  - UC
  - CD $\pm$ (limited use)
  - For life

What to do when Symptoms Come Back: Is this IBD, or Somthing Else?

- Infection
- Prenancy
- Drugs
- Other conditions (stress)
- Non-adherence to maintenance Rx
- Change in smoking habits

Is this a recurrence of IBD?

- 3-day D/C 5-ASA
- Double dose 5-ASA
- Possible use of antibiotics
- Start prednisolone 40 mg (AEs) for 2 weeks, then taper
- Call your "GI, "GIM" or "GS"
  - If no response, or quick return symptoms with taper

Abbreviations: AE, adverse effects; D/C, discontinue; GI, gastroenterologist; GIM, general internal medicine specialist; GS, general surgeon

---

Is this a Severe Recurrence of Symptoms?

➢ > 6 BM/day
➢ Blood
➢ Pain, malaise
➢ Fever
➢ Extraintestinal symptoms: e.g. Arthralgias, Aphthous
  Ulcers, rash

Are you using GCS appropriately?

➢ Moderate severe disease
➢ Warn about side effects!
➢ Caution about short term use only
➢ Inform about escape from steroid-dependency and
  resistance
➢ Use locally acting Entocort® for SB/C-CD
➢ Dexa scan and bisphosphonates

Should An Immunosuppressant be used?

➢ CyA-UC

➢ In acute UC (not CD), a bridge to maintenance
  therapy

➢ Requires AZA

➢ Is the colon worth saving?

➢ Deaths

Immunosuppressants in Crohn's disease

➢ Why are you not using immunosuppressant?

➢ Steroid-resistant/-dependent

➢ Maintenace therapy

Is there a good reason to use experimental biological therapy?

- Failed standard medical therapy: 5-ASA→GCS→AZA/MTX
- Willing, informed patient
- Adequate medical insurance to provide for long term use

What wil the referral MD likely do?

- Confirm the diagnosis
- R/O
  - Infections (stoll cultures)
  - Obstructions (abdominal firm)
  - Abcess (ultrasound, MRI)
- Full dose 5-ASA, start on prednisolone
- Judicious decision re: "scoping"
- Consider anti-TNF therapy for failed AZA, MTX

Abbreviations: AZA, azathioprine; MTX, methotrexate

IS the diagnosis of IBD correct?

- Suspect, diagnosis from symptoms and signs (GI, non-GI)
- Compatible x-ray or endoscopic changes
- Compatible or diagnostic biosy
- Indeterminate, UC, Crohn's
- For some, only time will tell

Is it important to distinguish between Crohn's disease and Ulcerative Colitis?

- Crohn's – mouth to anus
  - Malabsorption
  - RLQ Mass
  - Perianal disease
  - Fistulae
  - Skin lesions
- Ulcerative Colitis
  - Bleeding
  - Dilation

Is it important to distinguish between Crohn's and Ulcerative Colitis?

- ➤ Acute
  - o UC-CyA
  - o CD-TNFβ
- ➤ Maintenance
  - o UC-5-ASA
  - o CD-AZA/MTX
  - o Surgery

Do patients with IBD ever have IBS-like symptoms?

- ➤ IBS-like symptoms shouldn't be treated as IBD
  - o Anti-diarrheal agents
  - o Anti-cholinergic agents
  - o Anti-biotics
  - o Bile acid sequestrants
  - o Anlgesics
  - o Exercise caution when/if using analgesics

"Tips on staying on top®" of IBD

- ➤ Causes of chronic diarrhea
- ➤ Distinquish between
  - o IBS & IBD
  - o UC & CD
- ➤ Standard first line therapy
- ➤ What causes recurrence of symptoms

Any Last Minute Questions about Therapy in Crohn's disease: Suggestions?

- ➤ Less use of 5-ASA, antibiotics
- ➤ More use of Imuran, methotrexate
- ➤ Appropriate cautious use of TNFβs

Chapter 10: Scientific Basis of Colonic Disorders

G.K. Turnbull, M. Burnstein,
J.A. Rowe and S.J. Vanner

1. Introduction

This chapter presents an overview of colonic physiology and the diseases that affect the colon. It discusses lower gastrointestinal bleeding, infectious diseases affecting the colon and diseases specifically involving the anus.

2. Function

The colon contributes to three important functions in the body: (1) concentration of fecal effluent through water and electrolyte absorption, (2) storage and controlled evacuation of fecal material and (3) digestion and absorption of undigested food. Although the colon is not essential for survival, its functions contribute significantly to the overall well-being of humans. The colon can be functionally divided through the transverse colon into two parts, the right and left colon. The right colon (cecum and ascending colon) plays a major role in water and electrolyte absorption and fermentation of undigested sugars, and the left colon (descending colon, sigmoid colon and rectum) is predominantly involved in storage and evacuation of stool.

3. Functional Anatomy

The human colon is a muscular organ measuring approximately 125 cm in length *in vivo*. Figures 2 and 3 show images of a normal colon at colonoscopy. Its wall consists of the four basic layers found in other GI hollow visceral organs – the mucosa, submucosa, circular muscle and longitudinal muscle – but several important differences exist. The mucosa lacks the villous projections found in the small intestine and presents a relatively smooth surface, but numerous crypts extend from its surface. Cell types lining the surface and the crypts resemble those in the small intestine but are composed of significantly greater numbers of goblet cells. These cells secrete mucus into the lumen, and mucus strands can often be identified in association with stool. This observation is misconstrued by some patients as a response to underlying colonic pathology. The haustral folds, which help define the colon on barium x-ray, are not a static anatomical feature of the colon but rather result from circular muscle contractions that remain constant for several hours at a time. The outer or longitudinal muscle is organized in three bands, called taeniae coli, which run from the cecum to the rectum where they fuse together to form a uniform outer muscular layer. These muscular bands and elongated serosal fat saccules, called appendices epiploicae, aid in the identification of the colon in the peritoneal cavity.

The colon is innervated by the complex interaction of intrinsic (enteric nervous system) and extrinsic (autonomic nervous system) nerves. The cell bodies of neurons in the enteric nervous system are organized into ganglia with interconnecting fiber tracts, which form the submucosal and myenteric plexi. These nerves are organized into local neural reflex circuits, which modulate motility (myenteric), secretion, blood flow and probably immune function (submucosal). Serotonin (5-HT), released from enterochromaffin cells into the surrounding lamina propria, is an important signaling pathway to these nerves in response to chemical and mechanical stimuli.

Release of excitatory neurotransmitters such as acetylcholine, substance P and serotonin (5-HT) serves to activate local circuits such as those innervating muscle contractions. Their receptor subtypes provide pharmacological targets for the development of drugs designed to alter colonic functions such as motility. The major inhibitory neurotransmitter is nitric oxide. The importance of the enteric nervous system is exemplified by Hirschsprung's disease, where there is a congenital absence of nitric oxide – containing inhibitory neurons over variable lengths of the rectum and colon. This results in an inability of the colon to relax in the affected region.

Infants typically present with bowel obstruction or severe constipation. Barium x-rays identify the affected region as a constricted segment because the excitatory effects of the neurotransmitter acetylcholine are unopposed as a result of the absence of inhibitory neurotransmitter.

The autonomic nervous system comprises sensory nerves, whose cell bodies are found in the dorsal root ganglia, and motor nerves, the sympathetic and parasympathetic nerves. Parasympathetic nerves innervating the right colon travel in the vagus nerve, and those innervating the left colon originate from the pelvic sacral nerves. Parasympathetic nerves are predominantly excitatory, and sympathetic nerves are inhibitory. Autonomic nerves modulate the enteric neural circuits within the colon and participate in neural reflexes at the level of the autonomic ganglia, spinal cord and brain. Brain–gut connections are important both for perception of visceral stimuli (sensory) and in modifying colonic function (motor) in response to central stimuli. An example of a central stimulus that can evoke significant changes in colonic activity through this connection is acute stress. This stimulus provokes release of central hormones, such as corticotropin releasing factor. These hormones activate parasympathetic pathways that stimulate motility patterns in the colon, and can result in diarrhea.

4. Absorption and Secretion

The colon is highly efficient at absorbing water. Under normal physiological conditions, approximately 1.5 L of fluid enters the colon each day, but only about 100–200 mL is excreted in the stool. The maximal absorptive capacity of the colon is up to about 4.5 L per day, so that diarrhea (increased water in stools) will not occur unless the ileocecal flow rate exceeds the absorptive capacity and/or the colonic mucosa itself is secreting fluid. The fundamental feature of colonic electrolyte transport that enables this efficient water absorption is the ability of the colonic mucosa to generate a large osmotic gradient between the lumen and the intercellular space.

This osmotic gradient is created by electrogenic sodium transport. This depends upon the energy-dependent Na+/K+-ATPase pump on the basolateral membrane, which pumps sodium from inside the cell against a large concentration gradient into the intercellular space (see Figure 6 in Chapter 6, "The Small Intestine"). Luminal sodium in turn enters the apical membrane of the cell through sodium channels, flowing down the concentration gradient created by the Na^+/K^+-ATPase pump. In contrast to the small intestine, where sodium in the intercellular space can diffuse back into the lumen and become iso-osmotic, hypertonic solutions are maintained in the intercellular space of the colon because the tight junctions are much less permeable to sodium diffusion. The net result is that the hypertonic fluid within the intercellular space draws water passively into the mucosa from the colonic lumen. In the colon there is also a highly efficient absorption of sodium (Na^+): of the 150 mEq of Na^+ that enters the colon each day, less than 5 mEq is lost in the stool. In contrast to Na^+, the tight junctions of the colon are highly permeable to potassium (K^+), allowing K^+ to move from the plasma to the lumen. K^+ pumped into the colonocyte by the Na+/K+-ATPase pump can also be secreted into the lumen. K^+ is normally secreted into the lumen unless intraluminal potassium rises above 15 mEq/L. This handling of potassium may account for hypokalemia seen with colonic diarrhea and may play a role in maintaining potassium balance in the late stages of renal failure.

Other transport mechanisms, similar to those found in the small intestine (see Chapter 6, Section 5), are also found on colonocytes, which maintain electrical neutrality, intracellular pH and the secretion of salt and water. Nutrient cotransporters, however, are not found in the colon.

The regulation of water and electrolyte transport in the colon also involves the complex interplay between humoral, paracrine and neural regulatory

pathways (see Chapter 6). One important difference is the effect of the hormone aldosterone, which is absent in the small intestine. Aldosterone is secreted in response to total body Na+ depletion or K+ loading, and in the colon, aldosterone stimulates sodium absorption and potassium secretion.

5. Motility of the Colon

Much less is known about the motility of the colon as compared to other regions of the GI tract. The movement of fecal material from cecum to rectum is a slow process, occurring normally over 3-4 days. Functionally, the contraction patterns in the cecum and ascending colon cause mixing, which facilitates the absorption of water, whereas in the sigmoid colon and rectum the contraction slow the movement of formed stool, forming a reservoir until reflexes activate contractions to advance and evacuate stool.

Several contractile patterns exist within the circular and longitudinal muscle of the colon. Ring contractions are due to circular muscle contraction, and these are either tonic or rhythmic. Tonic contractions are sustained over hours, form the haustral markings evident on barium x-rays and play a role in mixing. Rhythmic ring contractions are either intermittent or regular. Regular contractions are nonocclusive, occur over a few seconds, and migrate cephalad (right colon) and caudad (left colon). Presumably, they too play a role in mixing. Intermittent ring contractions occur every few hours, occlude the lumen, and migrate caudad. They result in the mass movement of stool, particularly in the sigmoid colon and rectum.

Contractions of the longitudinal muscle produce bulging of the colonic wall between the taeniae coli, but the physiological importance of this action remains poorly understood. The origin of the contractions of the longitudinal muscle is not completely understood, but it depends upon the slow wave frequency of smooth muscle.

Action potentials occur on the peaks of these membrane oscillations and hence they control the frequency of contractions. These slow waves originate in the interstitial cells of Cajal (ICCs), which serve as the pacemakers. This network of ICCs is interposed between the enteric nerves and the smooth muscle cells. Contractions are also modulated by paracrine, humoral and other neural pathways. The nature of the contractile patterns within the colon depends upon the fed state. This is best exemplified during eating when the "gastrocolic reflex" is activated. Food in the duodenum, particularly fatty foods, evokes reflex intermittment rhythmic contractions within the colon, and corresponding mass movement of stool. This action, which is mediated by neural and humoral mechanisms, accounts for the observation by many individuals that eating stimulates the urge to defecate.

6. Digestion and Absorption of Undigested Food Products

Greater numbers of bacteria (more anaerobes than aerobes) are found within the colonic lumen (10^{12-14}) than elsewhere in the GI tract. These bacteria digest a number of undigested food products normally found in the effluent delivered to the colon, such as the complex sugars contained in dietary fiber.

Complex sugars are fermented by the colonic bacteria, forming the short-chain fatty acids (SCFAs) butyrate, propionate and acetate. These SCFAs are essential nutrient sources for the colonic epithelium, and in addition SCFAs provide up to 500 cal/day of overall nutritional needs. They are passively and actively transported into the colonocytes where they become an

important energy source for the cell through the β-oxidation pathway. The importance of this role of SCFAs is illustrated by the effects of a "defunctioning" colostomy, which diverts the fecal stream from the distal colon. Examination of this area devoid of luminal content typically reveals signs of inflammation, termed *diversion colitis*. This inflammation can be successfully treated with the installation of mixtures of SCFAs into the rectum, thereby providing the necessary energy source for the colonocytes.

Fermentation of sugars by colonic bacteria is also an important source of colonic gases such as hydrogen, methane and carbon dioxide. These gases, particularly methane, largely account for the tendency of some stools to float in the toilet. Nitrogen gas, which diffuses into the colon from the plasma, is the predominant gas. However, the ingestion of large quantities of undigested complex sugars such as found in beans of the maldigestion of simple sugars such as lactose can result in large increases in production of colonic gas. This can lead to patients' complaints of abdominal bloating and increase flatus.
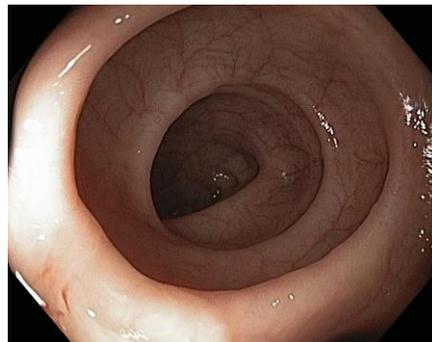
1A **1B**

Figure 1. Normal colon appearance at endoscopy.
Figure 1A. View of the normal submucosal vessels visible through the healthy transparent mucosa overlying the vessels.
Figure 1B. Normal transverse colon with a triangular appearance to the normal colon fold pattern
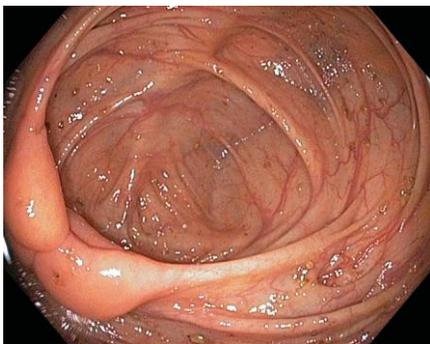
Figure 2. Normal ileocecal valve seen in the bottom left of the image, looking down at the cecal pole.

Bile salts are normally absorbed in the ileum, and long-chain fatty acids (LCFAs) in the upper small intestine. When bile salts or long-chain fatty acids are malabsorbed in sufficient quantities, their digestion by colonic bacteria generates potent secretagogues.

Bile salt malabsorption typically occurs following resection of less than 100cm of the terminal ileum, usually for management of Crohn disease. The excess bile salts pass into the colon where they stimulate cAMP and cause a secretory "choleraic" diarrhea. When the resection involves segments greater than 100 cm of ileum, the liver cannot sufficiently increase the synthesis of bile acids from cholesterol. A deficiency of bile acids enters the duodenum and if the concentration of bile acids is below the critical micellar concentration, bile salf micelles do not form, lipids are malabsorbed, and "fatty" Diarrhea (known as steatorrhea) develops.

The mechanisms by which multiple metabolites of bile salts and hydroxylated metabolites of long-chain fatty acids act as secretagogues provide an example of how multiple regulatory systems can interact to control colonic function. These mechanisms include disruption of mucosal permeability, stimulation of chloride and water secretion by activating enteric secretomotor neurons, enhancement of the paracrine actions of prostaglandins by increasing production, and direct effects on the enterocyte that increase intracelluar calcium.

Non-pathogenic bacteria also signal to mucosal cells and can evoke cytokine signaling from colonocytes to effector cells (e.g. immune cells, nerves) within the colonic wall. Some species of bacteria stimulate pro-inflammatory responses whereas others are anti-inflammatory. These signaling pathways are enhanced when the tight junctions between epithelial cells are altered. These tight junctions are formed by proteins (e.g., occludens) and can be disrupted by a growing list of processes, e.g., inflammation such as Crohn disease and also noninflammatory states such as acute stress. This increased leakiness or permeability of the colon allows bacteria greater access to the epithelium and immune cells in the lamina propria. This bacterial-epithelial signaling underlies the rationale for the use of probiotics where "healthy" or anti-inflammatory bacteria are ingested (e.g., lactobacillus, bifobacteria) and alter the dynamic between the competing species of bacteria.

7. Imaging of the Colon / J.A.Rowe

A variety of modalities can be used to image the colon, depending on the person's clinical presentation. Traditionally, patients presenting acutely with abdominal pain would have conventional radiographs (views of the abdomen) before any further cross sectional imaging was performed. It is now quite common for patients to undergo either abdominal CT or ultrasound as their initial investigation. For patients requiring outpatient imaging for evaluation of abdominal pain, rectal bleeding, anemia or change in bowel habits, investigations may include barium imaging, ultrasound, endoscopic ultrasound (EUS), abdominal CT, or MRI. Specialized applications of ultrasound and MRI are used in preoperative staging of rectal cancer and in the imaging evaluation of fecal incontinence.

7.1. Conventional Radiography/Plain Films

Conventional radiography, or the abdominal series, includes a supine, erect or decubitus view and an image that includes the lung bases. This allows evaluation of the intestinal gas pattern and the presence of free air. A single supine view of the abdomen or 'flat plate' is used to evaluate for the presence of excessive amounts of stool. Patients with abdominal pain will often require imaging beyond the plain film. While a radiograph can be useful in the evaluation of the potential presence and level of obstruction, adynamic ileus, or pneumatosis intestinalis. Widespread use of CT and ultrasound has significantly decreased the demand for conventional radiography, particularly in the acute setting.

3A

3B

3C

Figure 3. Plain x-rays of the abdomen showing normal supine and erect views of the abdomen.

Figures 3A. and 3B. are supine films and

Figure 3C. Eerect film of the abdomen.

7.2. Barium Imaging

Imaging of the colon has been traditionally achieved by performing a barium enema. Early in the 20th century, the single contrast technique was developed. An adequately cleansed colon is an important part of the examination. A bowel preparation will include a low residue diet for 1-2 days prior to the examination and a cathartic preparation. A tube is placed in the rectum and the colon is distended with a large volume of low density barium. Multiple spot images are obtained of the various colonic segments to visualize the entire colon free from overlapping loops. Later in the 20th century, the double contrast barium enema technique was developed. It involves the introduction of a small volume of high density barium through a small rectal tube, followed by insufflation of a large volume of room air, allowing good colonic distention and mucosal coating of the barium.

Some institutions routinely use pharmacologic agents such as glucagons, or the anticholinergic buscopan, to induce colonic hypotonia. However, a technically adequate study

can usually be obtained without these agents. The goal of the double contrast barium enema is to evaluate each portion of the colon in air contrast and with the barium pool. Compression can be used to manage overlapping bowel loops. A series of spot images during fluoroscopic evaluation and subsequent standard series of abdominal radiographs performed by the technologist comprise a complete examination.

A single contrast enema may be adequate for the detection of larger colonic lesions, obstructing lesions, as well as the depiction of diverticular disease. A double contrast study is preferred for the assessment of mucosal abnormalities as well as the detection of small polypoid lesions. In particular, the findings of inflammatory bowel disease involving the colon are well depicted on a double contrast study. Figure 4 is a single contrast enema demonstrating multiple colonic diverticula (white arrow). Figure 5 is a single contrast study demonstrating a large cecal mass which proved to be an adenocarcinoma. Figure 6 is a double contrast barium enema showing multiple diverticula as well as a subcentimeter polyp (white arrow) which proved to be a tubular adenoma. Figure 7 is a double contrast barium enema in a patient with ulcerative colitis depicting granular mucosa with some ulceration.
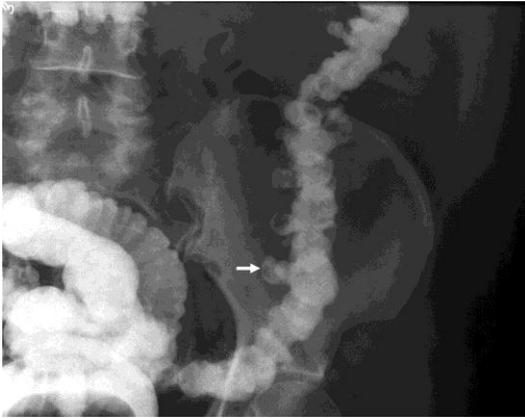
Figure 4. Single contrast enema demonstrating multiple colonic diverticula (white arrow).
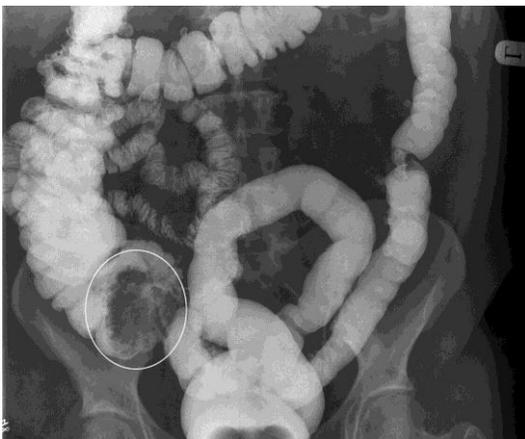
Figure 5. Single contrast study demonstrating a large cecal mass which proved to be an adenocarcinoma.

Figure 6. Double contrast barium enema showing multiple diverticula as well as a subcentimeter polyp (white arrow) which proved to be a tubular adenoma.

Figure 7. contrast barium enema in a patient with ulcerative colitis depicting granular mucosa with some ulceration from the distal transverse colon, beyond the splenic flexure and down the descending colon. The proximal transverse colon looks normal.

7.3. CT

Computerized tomography (CT) has become the primary imaging technique in patients who present with abdominal pain. This offers excellent evaluation of intramural and extracolonic pathology. The patient is given an overnight bowel preparation with positive oral contrast, to provide optimal evaluation of the colon, and is also given iodinated intravenous contrast at the time of CT scanning. In an urgent or emergent setting, the oral bowel preparation may be shortened or eliminated, positive contrast may be administered via the rectum. Unless there is a contraindication, intravenous contrast is recommended to evaluate the solid abdominal viscera, as well as to enhance the visualization of blood vessels and the bowel wall.

Common entities which are well characterized by CT include bowel obstruction, ischemia, ileus, malignancy, abscess, and diverticulitis. Figure 8 demonstrates sigmoid diverticulitis with a thick walled loop of sigmoid colon (white arrows) and extensive pericolonic stranding. A moderate amount of free intraperitoneal fluid is also present. Figure 9

demonstrates diffuse concentric wall thickening of the splenic flexure in a patient with ischemic colitis. Figure 10 shows markedly irregular bowel wall thickening identified by the black arrows involving the cecum, ileocecal valve, as well as the terminal ileum, in keeping with a primary adenocarcinoma.
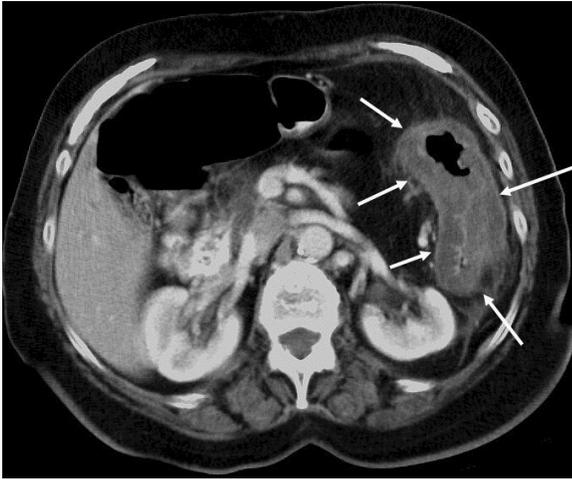
Figure 8. CT scan that demonstrates diffuse concentric wall thickening of the splenic flexure (white arrows) in this patient with ischemic colitis.

Figure 9. CT scan demonstrating diffuse concentric wall thickening of the splenic flexure (white arrows) in a patient with ischemic colitis.
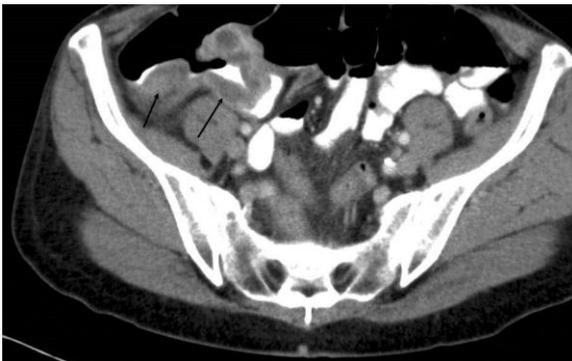
Figure 10. Shows markedly irregular bowel wall thickening identified by the black arrows involving the cecum, ileocecal valve, as well as the terminal ileum, in keeping with a primary adenocarcinoma.

7.4. CT Colonography

The barium enema has been a mainstay of colonic evaluation and can allow a diagnosis of neoplastic and inflammatory disease. The development of new technologies has highlighted the limitations of barium studies. While a barium study can evaluate the mucosa, it is unable to evaluate the lumen, bowel wall, and the extracolonic structures.

CT colonography (CTC), or "virtual colonoscopy," is a minimally invasive method of imaging the colon. CTC uses a thin section CT of the insufflated colon. The patient undergoes a standard bowel preparation. A catheter is placed in the rectum. Room air or carbon dioxide is insufflated to achieve optimal colonic distention. In the absence of contraindications, intravenous buscopan is injected to achieve optimal colonic distention. Imaging is performed in both the supine and prone positions. Post processing software allows evaluation of the axial 2D images and 3D reconstructions, or endoluminal flythrough.

While conventional "optical" colonoscopy with biopsy is the gold standard for the detection of colorectal masses, the CTC is less invasive, requires no sedation and has minimal recovery time. CTC offers the added benefit of evaluation of potentially significant extracolonic abnormalities. Advantages over barium enema include an increase in sensitivity and specificity for detection of significant polyps as well as cancer. The radiation dose is however higher than a standard barium enema. For patients who have undergone failed optical colonoscopy, a CTC can be performed on the same day to eliminate the need for a repeat bowel preparation. CTC can also evaluate the proximal colon in patients with a known obstructing cancer. Evaluation of lymph nodes, local invasion and evaluation for distant metastatic disease can also be performed with this exam. CTC can be safely used in the evaluation of elderly patients or other groups of persons who may be at increased risk for conventional colonoscopy. Anticoagulated patients, those with a past history of incomplete colonoscopy, or those who cannot undergo conscious sedation can be evaluated with CTC.

With the current body of research, it is widely accepted that CTC has been clinically validated and ready for use as an investigation and screening technique in patients of average and increased risk of CRC. Continuing developments in 3D visualization software and computer assisted detection algorithms improve the utility of this technique. CTC has been proven to have greater than 90% sensitivity for the detection of polyps > 10 mm, and close to 100% sensitivity for detecting CRC. CTC is quite well tolerated in comparison to barium enema or colonoscopy.

Developing techniques for screening for colonic polyps/CRC include fecal tagging, which may eliminate the need for a cathartic preparation (often the most difficult part of any technique which evaluates the colon). With fecal tagging, the patient ingests small amounts of barium or iodine with the bowel preparation. Any residual stool or fluid will be of higher density which will allow them to be distinguished from polyps or other soft tissue density filling defects. Figure 11A (axial source image) and figure 11B (endoluminal reconstruction) in a patient with incomplete colonoscopy demonstrates a large polypoid mass (black arrows) subsequently proven to be adenocarcinoma. The white arrows denote the ileocecal valve.

In many institutions, CTC has replaced barium enema as the first line modality in the investigation of lower GI tract symptoms. CTC has proven to be an accurate and reliable diagnostic and screening tool. Its use is limited only by its availability.

Figure 11 A. Axial source image

Figure 11 B. Endoluminal reconstruction These figures are from a patient with an incomplete colonoscopy demonstrated a large polypoid mass (black arrows) subsequently proven to be an adenocarcinoma. The white arrows denote the ileocecal valve.

7.5. MR Colonography

Still a developing technique, MR colonography (MRC) offers the potential for noninvasive evaluation of the colon, with the advantage of no ionizing radiation. As with CTC, the patient undergoes a standard bowel preparation. The patient is imaged in the prone position following colonic distension with 2500 ml of warm tap water introduced per rectum. Buscopan may be used to optimize colonic distension. Imaging is obtained pre- and post- gadolinium contrast enhancement, usually in the coronal plane. Imaging can be performed in a single breath hold. The data is evaluated on a workstation with both the source images and virtual endoscopic rendering of the lumen, allowing endoluminal flythrough. A combination of T1 and T2 weighted imaging provide bright and dark lumen colonography possible with one protocol. In addition to the evaluation of polyps and masses, MRC shows promise for the assessment of colonic

involvement in inflammatory bowel disease. Further work needs to be done to fully validate this technique however the results are promising.

7.6. Imaging of Fecal Incontinence

Fecal incontinence affects up to 10% of the adult female population, largely due to prior obstetrical trauma. Surgical options exist in the correction of this important problem, and preoperative imaging is often required to characterize the abnormality.

Endoanal ultrasound using a high frequency (10 MHz) endorectal probe is used to evaluate the anal sphincter complex. Ultrasound can identify the subepithelial tissue, the internal sphincter, the intersphincteric space, the longitudinal muscle as well as the external sphincter. This technique can confirm the presence or absence of sphincter defects. Ultrasound is also quite useful in the follow-up of the post surgical correction of fecal incontinence.

MRI is comparable to endoanal ultrasound in delineating sphincter anatomy, as well as any defects, which may contribute to fecal incontinence. Multiplanar T2 weighted images provide relevant anatomic information. Optimally, an endoluminal coil is ideal for demonstrating subtle changes in the sphincters, and provides the required spatial resolution. MRI is reasonably well tolerated, but takes longer than ultrasound to perform.

8. Fecal Incontinence

Understanding fecal incontinence requires knowledge of the normal function of the anorectum. Anatomically, the anorectum consists of the internal anal sphincter (IAS), the external anal sphincter (EAS), and the puborectalis muscles (PR). The IAS consists of smooth muscle and is a continuation of the circular smooth muscle of the rectum. The EAS is made up of skeletal muscle and surrounds the IAS, whereas the PR is a large U-shaped skeletal muscle that wraps around the upper anal canal at the anorectal

junction above the EAS, and loops anteriorly to attach to the pubic bone. This creates an anatomical sling of muscle that pulls the anorectal junction forward when it tightens, thus closing the upper anal canal and creating the anorectal angle that is vital to the maintenance of fecal continence.

When stool (or gas or liquid) enters the rectum or sigmoid colon, the bowel dilates, and a normal rectoanal inhibitory reflex (RAIR) or rectosphincteric reflex is initiated – that is, the IAS relaxes and, if the voluntary anal sphincter muscles also relax, the rectum empties through the anal canal (Figure 9). Fecal continence is maintained by anal contraction under voluntary control of the striated-muscle sphincters, the EAS and PR until the rectal pressure rise decreases and the resting tone of the IAS is restored. Thus, the "voluntary" sphincters (i.e., the EAS and PR) have the ability to be maximally contracted for approximately one minute, beyond which fecal continence is lost as a result of fatigue in the muscle if the tone of the IAS has not recovered.

Some patients with fecal incontinence will describe their problem as "diarrhea," rather than loss of control of bowel function. All patients with a complaint of diarrhea should be asked if they have lost control of stool (ie. If they have fecal incontinence, or "accidents"), as this may indicate where the problem actually lies. Once fecal incontinence has

been noted, it is then necessary to identify the frequency of the incontinence, whether both liquid and solid stool have been leaked, and whether the individual has an urge to defecate before the leakage occurs. A history of previous anorectal trauma (surgical, obstetrical, or otherwise) is important to note, as is the strength of voluntary anal canal tone on digital rectal exam (DRE).

Table 5. Drug therapy in irritable bowel syndrome

Symptom Drug Dosage
➢ Abdominal pain
  o Anticholinergics
    − Hyoscyamine 0.125 mg sl p4h prn (only available in US)
    − Dicyclomine 10–20 mg po tid – qid before meals
  o Calcium antagonists
    − Pinaverium bromide 50–100 mg po tid before meals
  o Antidepressants
    − Nortriptyline 10–25 mg po hs (increase by 10–25 mg increments every 5 to 7 days as tolerated)
  o Enteric opioids
    − Trimebutine 100–200 mg po tid before meals
    − Fedotozine NOT available in Canada

➢ Constipation
  o High fiber diet ε 30 g daily plus 2 L liquid daily
  o Osmotic laxatives
  o Milk of magnesia 15–30 mL po bid – tid
  o PEG 3350 powder 17 grams in 250 ml of liquid daily
  o Prokinetic agent
    − Tegaserod 6 mg po bid (NOT available in Canada)
  o Other agents
    − Misoprostol 200 μg po bid – qid before meals to stimulate diarrhea

➢ Diarrhea
  o Binding agent (resin)
    − Cholestyramine 4 g po once to four times daily
  o Antimotility agents
    − Loperamide 2–4 mg po prn (maximum dose 16 mg/day)
    − Diphenoxylate 2.5 mg po qid prn
    − Alosetron 1 mg po bid (only available in US by special access)

➢ Abdominal bloating, "gas" Simethicone up to qid prn

➢ Motility agents
  o Domperidone 10–20 mg po qid
  o Tegaserod 6 mg po bid (NOT available in Canada)

➢ Probiotics
  o VSL#3 1 cap po bid
  o Bio-K$^+$ 1 cap po bid

Most patients presenting with fecal incontinence have "idiopathic" fecal Incontinence. Fecal incontinence may occur as the result of childbirth, surgical trauma, or other causes.With childbirth, many women suffer occult sphincter injury to the anal sphincters, both the internal anal sphincter and the external anal sphincters, and child birth may also cause damage to the pudenal nerves. The injury is often not recognized at the time of childbirth, so the sphincter weakness and fecal incontinence only becomes symptomatic years later, presumably with atrophy of the muscles with aging. Similar injury occurs with the urinary sphincters, and many women with "idiopathic incontinence" resulting from childbirth injuries present years later with both urinary and fecal incontinence. Sphincter injury at childbirth is more likely to occur with the first baby, if the baby is more than 4,600 g (10 lbs), if the second stage of labour is prolonged, if there are forceps or vacuum extraction used to assist the delivery. If an episiotomy is done to prevent tearing into the sphincters, or if there was a posterior occiput presentation of the baby's head at delivery, there is an increased risk of anal sphincter injury.

Surgical trauma is the next most common cause of fecal incontinence. Surgery (ie. a vaginal hysterectomy) can put excess stretch on the pelvic floor nerves and muscles, causing injury that may lead to weakness of the anal sphincters. Another common source of fecal incontinence is disruption of the internal anal sphincter, either during a lateral internal sphincterotomy to treat an anal fissure or, more commonly, with the older "Lord's" procedure of forceful three- or four-finger dilation of the anal sphincter under anesthetic, where the extent of damage to the sphincters is not predictable. The finding of perineal descent can be noted on examination of the perineum when the patient is asked to strain. This perineal dissent is associated with weakness of the pelvic floor muscles, as well as disruption of the normal anatomy. This gives rise to a mechanical disadvantage affecting the sphincter mechanism. Perineal descent may be associated with a rectocele or, in female patients, with a uterine prolapse. Rectal prolapse can also accompany weakness of the pelvic floor muscles and give rise to fecal incontinence.

LEARNING POINTS:
- o Unless a careful history is taken, fecal incontinence (FI) may be confused with diarrhea
- o DRE (digital rectal examination) gives important information on possible causes of FI
- o Therapy is directed by diagnosis: if the use of bulking and anti-diarrheal agents is unsuccessful, or if there are not correctable anatomical abnormalities, then sufferers of FI may benefit from referral for further investigation and management with, for example, biofeedback training.

Therapy of fecal incontinence has improved over the past decade, primarily because of the introduction of biofeedback training. This technique allows the patient to practice tightening of the striated-muscle portion of the anal sphincter, usually with a surface electromyography (EMG) plug electrode held in the anal canal with audio and visual feedback that the patient can see and hear to encourage maximal contraction of these muscles. Increasing dietary fiber to help reduce the amount of liquid stool may help some patients, but if this increases stool frequency, the patient be better on a low fiber diet to help constipate the stool and reduce the chance of stool incontinence. Loperamide has been shown to increase the resting tone of the anal sphincters (especially the resting tone of the internal anal sphincter) and is a useful adjunct, especially if the stool frequency is increased. Cholestyramine may be useful when the patient has diarrhea or loose stool(s) since cholestyramine can make stool more solid (constipating effect).

Surgery is of greatest benefit in those patients who appear to have a mechanical problem, such as rectal prolapse or disruption of the anal sphincter. Surgery to correct perineal descent is often less helpful, since the muscle weakness that gives rise to the descent is not satisfactorily reversed by any of the surgical procedures currently used, and attempts to "suspend" the pelvic floor muscles cannot strengthen these muscles. Patients should refrain from excess straining if they have significant perineal descent, because this will serve only to worsen the pelvic floor muscle weakness.

9. Constipation

In the approach to a patient with constipation, it is first necessary to define what the patient means by the term. Many definitions exist, but the best clinical definition is that over 95% of the North American population has a stool frequency from three times a day to three times a week: therefore, patients
who have a bowel frequency less than three times a week would be defined as being constipated. Many patients will describe their stool as "constipated," meaning that the stool is hard or in pellets (scybalous), while other patients may have a stool frequency that falls within the "normal" range yet feel that their bowels have not completely emptied. This latter symptom is a frequent complaint of persons with IBS, and many patients with IBS will describe a constipated bowel habit (constipion - predominant IBD).

In Western culture the most frequent cause of constipation is an inadequate intake of dietary fiber. The concept of "fiber" has become quite confusing to many persons, with the increased emphasis on "oat fiber" for elevated cholesterol treatment. Many foods that people consider to be high in fiber (e.g., salads, lettuce, tomatoes and celery) are in fact mainly water, and some vegetables may actually aggravate their symptoms. Fiber consists of complex carbohydrates that are incompletely digested by the small bowel, and are then "digested" by colonic bacteria, liberating short-chain fatty acids (SCFAs) and gases (flatus) from fermentation. The SCFAs and flatus may provoke and aggravate many of the associated abdominal symptoms (e.g., abdominal pain, "gas" and bloating). Cereal grain fibers that have more insoluble fiber (as opposed to soluble oat bran fiber) are best to increase stool frequency. The insoluble fiber should be added gradually over 8 to 12 weeks up to a maximum daily dose of about 30 g. Other fibers, in the form of "bulk laxative" preparations containing psyllium (isphagula), methylcellulose, or sterculia may be added to wheat bran fiber in order to accomplish this level of 30g fiber per day, without completely altering a patient's diet.

Many patients who are constipated continue to pass dry, hard stool, despite an increase in dietary fiber, because they do not increase the water content of their diet. Fiber works in the gut by holding onto water and keeping the stool soft. In order to achieve this effect, the intake of liquids must be increased. For a 30 g/day fiber diet, it is recommended that patients drink eight 8 oz. glasses (i.e., 2 L) of non–caffeine-containing beverages per day. Secondary causes of constipation must be excluded. The patient with bowel obstruction can present with constipation. This possibility of organic disease should always be considered in a patient with the new onset of constipation after the age of 40 years (when the incidence of colon cancer rises).

A rarer cause of constipation is hypothyroidism. Not infrequently, patients with an underactive thyroid will present with the primary symptom of constipation. Hypercalcemia rarely reaches levels that produce constipation, but should always be considered, since this electrolyte disturbance can be a life-threatening disorder. Constipation in this setting is always resistant to therapy until the hypercalcemia is treated. Proctitis can present with a complaint of infrequent stool passage. This is due to the functional obstruction from spasm caused by the inflammation

of the rectum. The colon more proximally continues to produce formed stool, which cannot pass easily through the inflamed rectum. Proctitis will usually be associated with excess mucus production, with or without blood in the stool, and proctosigmoidoscopy will diagnose this entity.

Another cause of constipation is diabetes mellitus, which results in impaired colonic motility due to dietary factors, as well as autonomic neuropathy of the enteric nervous system, seen with long-standing diabetes mellitus. Patients with diabetes may also develop diarrhea, which again has been linked to the autonomic neuropathy.

Inactivity from whatever cause increases the likelihood of constipaion. This is presumed to be secondary to reduced colonic activity due to a low fiber intake. Severe cardiopulmonary diseases of whatever cause that limit activity can also result in constipation.

Neurologic disorders that cause the patient to have a reduced ability to ambulate can have constipation as a feature. Some patients with diseases of the nervous system may have impaired awareness of rectal distention to signal a need to defecate, and nerve dysfunction (both peripheral and central) may impair normal colonic propulsion.

Finally, the elderly may develop problems with defecation. Although constipation with fecal impaction occurs they may complain of "diarrhea" or "soiling" due to overflow incontinence of stool from the fecal impaction of the rectum inhibiting the normal resting tone of the anal sphincter. Not surprisingly, many of these patients may respond to laxative therapy after the fecal impaction is removed, since this prevents the recurrence of the fecal impaction with overflow incontinence.

Some patients can aggravate longstanding constipation with regular laxative abuse, and some theoretical concerns remain that this practice may indeed damage the normal innervation of the colon, rendering it atonic and nonfunctional.

The physical findings are often minimal in the majority of patients with constipation, but specific secondary causes must be looked for. Signs of hypothyroidism may be present; signs of dehydration should be sought, as this may be an early indicator of hypercalcemia. Thorough cardiopulmonary and neurologic examinations are necessary to pick out associated diseases that may be treated, thereby improving the patient's overall health, and thus improving bowel function and the quality of their lives. On abdominal examination, inspection for evidence of distention, hyperperistalsis or masses may point t the source of the impaired stool passage. Localized tenderness of the abdomen must be noted, along with any evidence of liver, spleen or renal enlargement. A complete digital rectal examination and proctosigmoidoscopy is required in any patient with constipation so that the presence or absence of a fecal impaction, dilation or enlargement of the rectum or the presence of proctitis can be determined.

Pelvic Floor Dyssynergia

The majority of patients with constipation have a form of irritable bowel Syndrome. But, there is a small subgroup of patients who may have a specific disorder in colonic and/or anorectal function that produces constipation. These patients are almost always female, have delayed colonic transit, have anorectal dysfunction with impaired awareness to rectal distention, but no megarectum, or may have rectal outlet obstruction due to inappropriate contraction of the voluntary anal sphincters during defecation. This has been termed pelvic floor dyssynergia or anismus. These patients can present major therapeutic dilemmas, and warrant further investigation in specialized coloproctology units.[JW1]

10. The Anal Canal / M. Burnstein
10.1. Functional Anatomy of the Anal Canal and Anorectal Spaces
10.1.1. The Anal Canal

The anal canal begins where the terminal portion of the large bowel passes through the pelvic floor muscles, and it ends at the anal verge. It measures roughly 4 cm in length, usually longer in men than women. The wall of the anal canal is formed by a continuation of the circular muscle of the rectal wall; the smooth muscle is thickened in this area to form the internal anal sphincters (IAS). This smooth-muscle sphincter is wrapped by skeletal muscle, the external anal sphincter (EAS). The top of EAS is formed by the U-shaped puborectalis muscle, which loops around the anus, arising and inserting on the pubis. This is felt posteriorly and laterally as the anorectal ring on digital examination. The longitudinal muscle coat of the rectum descends in the plane between the sphincters as the conjoined longitudinal muscle, and it sends fibers across the lower part of the EAS to insert on the skin (corrugator cutis ani, responsible for the anocutaneous reflex or "anal wink"). These fibers also traverse the IAS to insert on the submucosa ("mucosal suspensory ligament" or Treitz's muscle).

In approximately the mid-anus there is a rolling line of demarcation called the dentate line. Above the line is columnar epithelium; below it is squamous epithelium without appendages (the anoderm). The demarcation does not really occur at a line, but at a transitional zone of 0.5–1 cm in length.

As the rectum narrows into the anal canal, the mucosa develops 6 to 14 longitudinal folds, Morgagni's columns. Between the distal ends of the columns are small crypts. Anal glands open into the crypts. There are 4 to 10 glands, and they are lined by stratified columnar epithelium. About half of these tubular glands end in the intersphincteric plane. Blood is supplied to the anus via the inferior rectal artery, a branch of the internal pudendal artery. The inferior rectal artery crosses the ischiorectal fossa. The superior rectal vein drains the upper part of the anal canal via the inferior mesenteric vein to the portal vein. The middle and inferior rectal veins drain the upper and lower anal canal into the systemic circulation via the internal iliac and internal pudendal veins, respectively. Lymphatic drainage above the dentate line is via the superior rectal lymphatics (accompanying the superior rectal vessels) to the inferior mesenteric nodes, and laterally along the middle and inferior rectal vessels to the internal iliac nodes. Lymphatic drainage from the anal canal below the dentate line may be in a cephalad or lateral direction, but is primarily to the inguinal nodes. Motor innervation of the EAS is via the inferior rectal branch of the pudendal nerve as well as the perineal branch of the fourth sacral nerve.

The IAS has sympathetic (motor) and parasympathetic (inhibitory) innervation. Parasympathetic supply is from the nervi erigentes (S2, S3, S4). Sympathetic innervation is from the first three lumbar segments via the preaortic plexus. Fibers from the preaortic plexus ultimately join the nervi erigentes to form the pelvic plexuses. Sensation below the dentate line (and for up to 1.5 cm above the dentate line) is carried by the inferior rectal nerve. Above the level of the inferior rectal nerve sensory distribution, there are only dull perceptions, mediated by parasympathetic fibers.

10.1.2. Anorectal Spaces

Around the anorectum there are a number of potential spaces filled with fat or connective tissue. These may become the sites of abscess formation. The perianal space is at the anal verge, and is continuous with the intersphincteric space. The pyramid-shaped ischiorectal (ischioanal) fossa is medially bounded by the EAS and the levator ani muscles. The lateral wall is the

obturator internus muscle and fascia. The inferior boundary is the skin of the perineum, and the apex is the origin of the levator ani from the obturator fascia. Posteriorly is the gluteus maximus muscle, and anteriorly the transverse perinei muscles. On the obturator fascia is Alcock's canal, containing the internal pudendal vessels and pudendal nerve. The fossa is filled with fat, and contains the inferior rectal nerve and vessels, as well as the fourth sacral nerve. The two ischiorectal spaces communicate with one another behind the anal canal via the deep post-anal space.
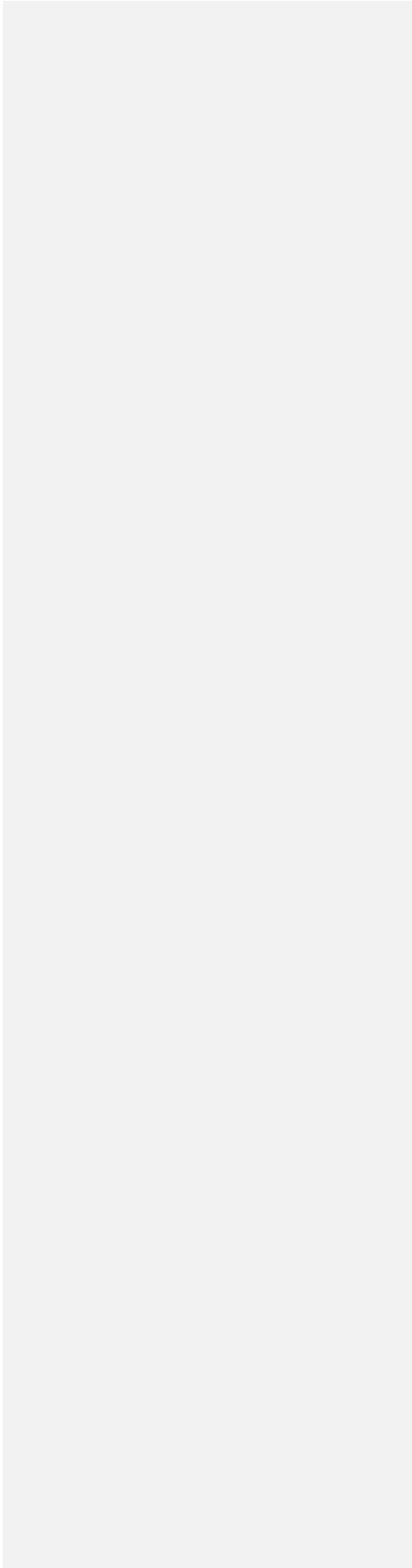
Chapter 11: Diverticulosis, Ischemia, Infection and Bleeding

G.K. Turnbull, M. Burnstein, J.A. Rowe and S.J. Vanner

1. Diverticulosis

In Western societies diverticulosis occurs in at least one person in two over the age of 50 years. The frequency increases with age. Diverticulosis or diverticular disease of the colon is due to pseudodiverticula in that the wall of the diverticulum is not full-thickness colonic wall, but rather outpouchings of colonic mucosa through points of weakness in the colonic wall where the blood vessels penetrate the muscularis propria.

These diverticula are prone to infection or "diverticulitis" presumably because they trap feces with bacteria. If the infection spreads beyond the confines of the diverticulum, an abscess is formed. Patients present with increasing left lower quadrant pain and fever, often with constipation and lower abdominal obstructive symptoms such as bloating and distention. Some patients with severe obstructive symptoms may describe nausea or vomiting. This can occur with or without abscess formation. Other causes of these symptoms include Crohn's colitis with stricture formation, colonic cancer, and ischemic colitis.

On physical examination the patient often has localized tenderness in the left lower quadrant (the most prevalent site of diverticulae). With severe infection and an abscess, examination may show rebound tenderness. A palpable mass is often identifiable in the sigmoid colon.

Treatment consists of intravenous fluids, bowel rest by placing the patient on no oral intake or just a clear liquid diet, and broad-spectrum intravenous antibiotics. Antibiotics selection should be to cover both gram-negative enteric bacteria and anaerobic bacteria that are normally found in the colon. CT scan may be helpful in outlining the colon and identifying an abscess, and is preferable to barium enema for diagnosis in patients with an acute illness.

Many complications can occur in diverticulitis. These are listed in Table 1. Colonic stricture after resolution of diverticulitis is described further in Section 3.3.

Bleeding occurs in less than 5% of diverticulosis patients; it is abrupt in onset, painless, and often massive. A bleeding diverticulum can be from either the left or right colon. Even though bleeding is more likely to occur in right colonic diverticulosis, the bleeding frequency is approximately equal because of the much higher frequency of left colonic diverticulosis. It is rare for patients with diverticulosis to have significant bleeding.

Table 1. Complications of diverticulitis

- o   Abdominal abscess/Liver abscess
- o   Colonic obstruction
- o   Fistulas
- o   Colovesical
- o   Colovaginal
- o   Colocutaneous

Over 80% of diverticulosis patients will stop bleeding spontaneously. The rest will continue and require investigation and treatment (see Section 5). Segmental colonic resection is reserved for that small group of patients who continue bleeding or have recurrent bleeding. Patients under the age of 40 with symptomatic diverticulitis should have surgical resection because this small subgroup is at greater risk of complications.
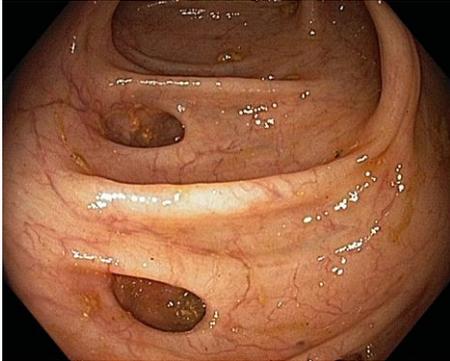
Figure 1A. The rounded openings of a several diverticulae are shown, with the colonic lumen at the top of the image.
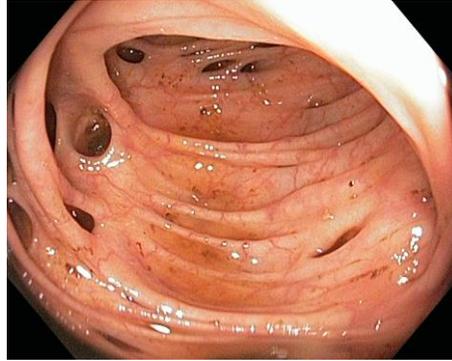
Figure 1B. Multiple diverticulum openings are shown, with the lumen at the upper half of the image. There is a larger opening to the left that can be confused with the lumen of the colon. With insertion of the colonoscope into a diverticulum, perforation

is the result.
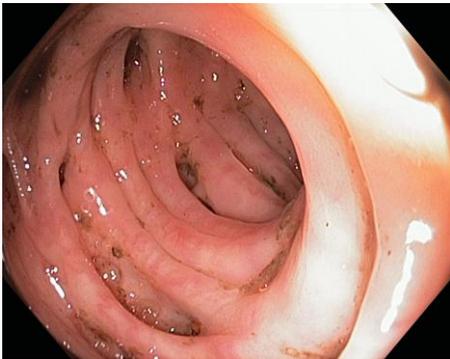
Figure 1C. The muscle in the sigmoid colon is hypertrophied with multiple diverticulum openings and the lumen towards the right of the image.

Figure 1. Examples of diverticulosis of the sigmoid colon at colonscopy.

2. Colonic Ischemia

Colonic ischemia is the most common form of intestinal ischemia. It tends to occur in older patients, but can occur at any age. Patients usually present with sudden onset of abdominal pain and rectal bleeding (see lower GI bleeding). The pain from colonic ischemia is often not as severe as in other cases of acute intestinal ischemia. The majority of cases of colonic ischemia are self-limited, associated with ischemia of the left colon and/or transverse colon where the "watershed" area of the colonic vasculature supply to the colon is. Most cases have mucosal ischemia with the muscular wall of the colon relatively less prone to ischemia. This prevents transmural ischemia in most cases.

Colonic ischemia may be associated with previous aortic surgery, usually because the inferior mesenteric artery that supplies much of the left colon arterial supply is sacrificed during these operations. Colonic ischemia is also associated with underlying diseases that may decrease colonic mesenteric blood supply due to low-flow states, as in hypotension related to surgery or other conditions that can lower blood pressure, or medications including drugs such as cocaine
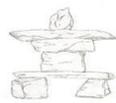
that induce vasospasm. Certain diseases are more commonly associated with colonic ischemia; diabetes, vasculitis, rheumatoid arthritis and amyloidosis. In younger individuals, colonic ischemia is often associated with extreme exertion as a long distance running (marathon running or triathalon competitions). Young women may be more prone to colonic ischemia, possibly because of their taking the "pill" (oral contraceptive agent), or from associated IBS (irritable bowel syndrome), which is more common in young women and which is associated with an unexplained increased risk of colonic ischemia. Colonic obstruction can also be associated with an increased risk of colonic ischemia, be from a malignant obstruction or diverticular disease. The mechanism is presumed to be from reduced blood flow to the colon as the result of torsion or stangulation of the bowel, or very high pressures in the colonic lumen. Infections have also been linked to ischemia, especially colonic infection with cytomegalovirus or *E. coli* O157; H7. Both of these release toxins that cause local vasospasm and thereby result in ischemia. Constipation, the use of opiates with their side effect of constipation and laxative use have all been associated with colonic ischemia.

Transmural ischemia and infarction of the colon occur in about 20% of cases. The factors predictive for a more serious form of colonic ischemia are: right-sided colonic ischemia or colonic ischemia affecting both the right and left portions of the colon, hypotension, tachycardia, use of anticoagulants, and male sex (even though the incidence is much higher in women). Rectal bleeding is a predictor of less serious colonic ischemia and the use of NSAIDs seemed to lower the risk of severe ischemia. Hypotension and tachycardia would both predict more extensive ischemia, depending on the duration of the shock. Warfarin use may identify patients with underlying cardiac or coagulation disorders who would be at greater risk for ischemia. Rarely, patients with severe ischemic colitis will pass a bowel cast which is the necrotic lining of the bowel. This finding only occurs in the sickest patients, usually when there is extensive necrosis and gangrene of the colon.
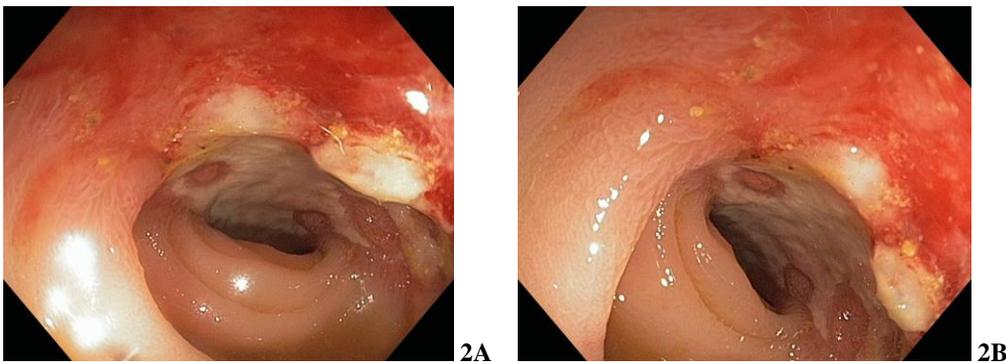
Figure 2. show ischemia of the colon at the splenic flexure where the mucosa in the near portion of the photos is just edematous but they there is ulcerated mucosa. On biopsy, the histology shows little inflammation and features indicating mucosa ischemia to distinguish this from ulceration at the splenic flexure from other diseases like Crohn's where the biopsies would show inflammation.

LEARNING POINTS:
- o Have a high suspicion for ischemia in the person who has severe abdominal pain, which is out of keeping with the absence of abnormal physical signs
- o Ischemia is more common in older persons, diabetics, those with coronary artery disease, irritable bowel syndrome, or persons on medications/drugs such as cocaine, OCA, or digitalis
- o If the ischemic bowel progresses to gangrene or perforation, emergency surgery is necessary

Treatment is mostly supportive but early recognition of extensive or severe ischemia is important in selecting out those few patients who are likely to have a severe outcome. If there is rectal bleeding, colonoscopy should be considered if the patient shows signs of peritoneal irritation, abdominal imaging should be done first to ensure that the patient has not already had a colonic perforation. Biopsies of the affected colon are often not helpful, in that the pathology can be non-specific, but biopsies may help to distinguish from other conditions that appear like colonic ischemia (ie. Crohn's colitis which can also cause a patchy ulcerating lesion of the colon, with the rectal sparing typically seen with ischemic colitis). If cytomegalovirus infection is suspected, colonic biopsy for viral culture is the most accurate way to identify this infection. Antibiotics may help as they have been shown to lessen the ischemic injury when used in animal models of colonic ischemia, but no clinical trials exist to support this practice. Steroids should be used with caution, because they may increase the colonic ischemia and increase the risk of perforation. Other anti-inflammatory therapies have not been evaluated, such as 5-ASA (mesalamine) therapies. These agents may have a role in patients who develop a chronic state of colonic ischemia, but this is also speculative.

Urgent surgery is when there is massive bleeding from colonic ischemia, if there is development of peritoneal signs, or evidence of toxic megacolon.

In patients with chronic colonic ischemia who do not improve over 2-3 weeks, especially if they develop a protein-losing enteropathy, surgery may be required. Surgery for strictures that develop after a severe case of colonic ischemia is best reserved for those patients who have definite symptoms of obstruction.

3. Infections of the Colon

3.1. Shigella

This infectious diarrhea is the classic cause of "bacillary dysentery." The typical presentation of a shigella infection is fever, abdominal cramping, and watery diarrhea that usually becomes bloody within 24 to 48 hours of onset. The incubation period of shigellosis is from 36 to 48 hours. As the disease progresses, the symptoms become typical of colonic dysentery, with small, frequent stools and cramping and tenesmus that may lead to rectal prolapse in some individuals with prolonged straining.

Shigella is a gram-negative bacterium with only humans as its host. The organism is well adapted to causing disease in humans. As few as 200 organisms are needed to cause infection, as

compared with other enteric infections requiring 10^6 organisms or more. Shigella can persist in food for weeks and on contaminated body surfaces for several hours. Pathogenesis is through production of a cytotoxin called Shiga toxin or similar toxins that are both cytotoxic and neurotoxic, very similar to the toxin produced by *E. coli* 0157:H7 species.

Shigella is a microinvasive bacterium that enters the host via the M cells in the intestine and then spreads laterally through the colonic mucosa to involve the basolateral membrane of the surrounding cells. It is seen mostly in travelers returning from endemic areas (tropical and subtropical). There is also a higher incidence of shigellosis in men who have sex with men (oral-anal sex). Treatment depends on the antibiotic resistance of the infecting strain of bacteria. Shigella species quickly develop antibiotic resistance. Patients should be encouraged to complete their course of antibiotics to prevent this.

Antibiotics shorten the duration of both symptoms and carriage of the organism. Untreated, shigella organisms can be excreted in stool for up to 6 weeks while the individual is asymptomatic. Fluoroquinolones are the antibiotics of choice because of the low incidence of resistance at present, but this may change. Ampicillin and trimethoprimsulfamethoxazole are also effective against sensitive strains. If infection has been acquired overseas, a confirmed Shigella infection is best treated with a fluoroquinolone twice daily for 5 days. There are reports of a single large dose eradicating infection (unless the organism is *S. dysenteriae* 1).

Antimotility agents such as loperamide, diphenoxylate or narcotic analgesics are contraindicated with this infection because of the risk of developing a toxic colon. In general, antimotility agents should never be used in acute infectious diarrhea when bloody stool is present.

3.2. Salmonella

Infection with nontyphoidal strains of Salmonella results from ingesting foods contaminated with these organisms. These bacteria are endemic to poultry and cattle populations. Large epidemics have resulted from undercooked eggs, and these bacteria are also frequently found in pet reptiles and amphibians. Salmonella contamination of marijuana can be an important infection source in young adults. Recent outbreaks have been from contaminated raw vegetables, especially salads and tomatoes. The usual incubation period is from 8 to 48 hours after ingestion.

S. typhi, which causes typhoid fever, is found only in humans. It will not be discussed further other than to emphasize that all Salmonella species are related, and therefore can cause systemic illness of similar severity, especially in persons who are immunocompromised and those at the extremes of age (i.e., those under 2 years and the elderly).

Salmonella is an invasive bacterium that can cause septicemia after first multiplying in the mesenteric lymph nodes. Our usual resistance to being infected with salmonella is a result of the presence of gastric acid, the integrity of the intestinal flora, and intestinal motility to clear the bacterium. Increased risk of salmonellosis is associated with the use of purgatives, antimotility agents, broad-spectrum antibiotics and acid-suppression therapy, previous bowel surgery will,

and diseases that predispose to infection as a result of impaired host defenses include sickle cell disease, systemic lupus erythematosus (SLE) and HIV/AIDS.

Treatment is usually symptomatic. Antibiotics should be used only if the patient is showing signs of bacteremia. Antibiotics often increase the development of a chronic carrier state. The antibiotics of choice are ampicillin, trimethoprim-sulfamethoxazole, the fluoroquinolones and the third generation cephalosporins (especially ceftriaxone, with its high biliary excretion) have been shown to be very effective in patients who need antibiotic therapy.

Treatment with antibiotics should normally be considered only for children under the age of 2 years or elderly persons with vascular disease.
Patients with metal implants in bones, lymphoproliferative disease, sickle cell disease, or HIV/AIDS. The site of chronic infection is usually the biliary tract. Disease of the biliary tree, especially cholelithiasis, requires surgery to correct the disease followed by a two-week course of therapy, which often leads to resolution of the chronic carrier state.

3.3. Clostridium Difficile

Many persons treated with antibiotics develop diarrhea (antibiotic-associated diarrhea), which stops when the antibiotic is discontinued. In a small portion of persons with AAD, there may be an infection with C. difficile. This spore-forming anaerobic gram-positive bacterium is the commonest cause of infectious diarrhea in hospitalized patients (nosocomical infection). C. difficile is not invasive, but with reduction of the normal colonic bacterial flora it multiplies, and produces two toxins, known as toxins A and B. Toxin A causes colitis. Toxin B is a cytotoxin that is often used as a diagnostic test for this infection.

Most commonly, infection is preceded by antibiotic therapy. Outbreaks in hospital frequently occur among the sickest patients, some of whom have not received antibiotics beforehand. Penicillins, cephalosporins and clindamycin are more likely to be associated with C. difficile infection, but all antibiotics, including metronidazole and vancomycin, have been associated with it. Antibiotics which have a lower risk of causing this infection are aminoglycosides, tetracycline, macrolides, sulfonamides and of course vancomycin. Other risk factors include agents that affect gut motility such as enemas, anti-diarrheal medications, and intensive chemotherapy. Acute flare-ups of colitis (ulcerative colitis or Crohn's colitis) can also be caused by C. difficile infection in persons who have not had prior antibiotic exposure. Patients with severe illnesses and advanced age are also more prone to manifest disease symptoms.

Diarrhea is the most common symptom of presentation, and is usually nonbloody. With prolonged diarrhea, some bleeding can result from local anorectal irritation. The typical appearance of a C. difficile infection at endoscopy of is of "pseudomembranes" or whitish plaques on the surface of the colonic mucosa, with intervening areas of mucosa that appear almost normal. For this reason, a C. difficile infection is often called "pseudomembranous colitis" (PMC), but PMC may occur in the absence of a C. difficile infection. Unfortunately, these characteristic changes may not always be present in the rectum or left side of the colon, so colonoscopy is needed to detect right colonic pseudomembranes.

The diagnosis of C. difficile is usually confirmed by the presence of cytotoxin in the stool placed on tissue culture. The clinician must be alert to the possibility of this infection in susceptible patients, since in some patients neither the culture of C. difficile nor the presence of the cytotoxin in the stool is positive. A careful inventory of any antibiotic therapy in the last three months is crucial in considering this cause for diarrhea, as many patients will have taken the offending antibiotic several days to weeks before symptoms begin.

Metronidazole treatment is preferred to vancomycin (unless the more virulent strain NAP1 is suspected – see below) because both antibiotics show similar efficacy in treating this infection and metronidazole is about one-tenth the cost of vancomycin. Treatment with metronidazole is for 10 to 14 days, usually in a dose of 500 mg p.o. t.i.d. The vancomycin dosage is 125 mg p.o. q.i.d. also for 10 to 14 days. It is effective only via the oral route, whereas metronidazole is also effective when given intravenously, as may be necessary in the occasional patient with postoperative ileus. With both regimens, there is a high relapse rate (up to 20%) of symptomatic infection.

The best method to prevent relapse is unknown, but relapsing symptoms may respond to retreatment of the infection with either metronidazole or vancomycin. There may be a role for the use of probiotics to prevent or to treat C. difficile. There has been emergence of a more virulent strain of C. difficile, called NAP1, which has a high mortality rate. NAP1 is often acquired in hospital rather than in the community, and is usually resistant to metronidazole. Therefore, patients who are very ill at presentation, with elevated white blood cell counts (>20,000), with fever and an elevated serum creatinine concentration should be started on vancomycin immediately rather than on metronidazole. The patients can have a decrease in diarrhea even though they are developing toxic megacolon. For this reason, NAP1 patients should always be monitored closely for the development of megacolon.

Another cause of AAD is right-sided hemorrhagic colitis from infection with *Klebsiella oxytoca*. Klebsiella oxytoca usually occurrs after treatment with penicillin antibiotics (especially amoxicillin-clavulanate). This infection should be considered in individuals who appear to have *C. difficile* infection, but their stool cultures are negative for the organism or its toxin. *K. oxytoca* is identified by stool culture, but it has to be specifically cultured for or it will be missed on routine stool culture.

3.4. Entamoeba Histolytica (Amebiasis)

Entamoeba histolytica, the parasite that causes amebiasis infection is the only ameba that causes disease in humans. Other amebas are often found in the colon as normal commensals. E. histolytica is a cyst-forming parasite, but the cysts do not cause disease. The cysts are ingested and are resistant to destruction by gastric acid, and so pass to the colon. From the cysts in the colon, trophozoites develop from the ingested cyst. The trophozoites invade the colonic mucosa and cause disease, but trophozoites passed in the stool of symptomatic individuals cannot survive outside the body and rarely transmit infection. The cysts spread disease to others, and frequently unaffected carriers spread disease by excreting cysts. The disease is most prevalent in areas of

the tropics where sanitation is poor. The amebae infect the colon and rarely the ileum, but the cecum is usually involved. The colonocytes are the initial site of disease. Invasion of the mucosa by trophozoites is due to the production of an "amebapore" molecule that causes the colonocytes to lyze. The lyzed colonocytes are then ingested by the amebas, leading to ulceration of the colon. E. histolytica is an invasive pathogen and can spread hematogenously to other organs, especially the liver, and can lead to dissemination of the infection throughout the body.

The diagnosis of amebiasis is usually made by identification of E. histolytica on microscopic analysis of stool, but can also be made on identification of the ameba on histological examination of colonic biopsies. There is a decreased yield on stool analysis after barium studies or if antibiotics or mineral oil has been used prior to the collection of stool samples for culture. Diagnosis can also be made by indirect hemagglutination and ELISA tests on serum to detect infection, but if the patient is a carrier with only cyst excretion these tests are often negative. At colonoscopy the ulcers of the rectum and colon may have characteristic undermined edges. Sometimes the intervening mucosa looks normal in contrast to acute bacillary dysentery (see Section 3.7.1) and ulcerative colitis.

Chronic infection of the cecum with E. histolytica leads to a "coned" appearance on x-ray. Other colonic complications include perforation, ameboma (a granulomatous tissue reaction in the colon; the ameba mass can lead to obstruction or be mistaken for colonic malignancy), pericolic abscess and fistulas.

The liver is the commonest extra-intestinal organ infected, but E. histolytica can also spread to the brain, lungs, pericardium and eyes. There is an increased risk of disseminated disease and abscess formation if the patient is on steroids, is pregnant or is immunocompromised.

Treatment for acute amebic colitis is with metronidazole 500 (400–750) mg t.i.d. for 5–10 days. If the patient has chronic colonic disease with chronic shedding of cysts, diloxanide 500 mg t.i.d. for 10 days is the drug of choice. If diloxanide cannot be obtained, then paramomycin 25 – 30 mg/kg/day divided into three equal doses per day for 7 days, or iodoquinol 650 mg t.i.d. for 20 days can be used. Exceeding this maximal dose my cause optic neuritis.

Patients with amebic liver abscess should first be treated with metronidazole for 10 days, and then be given 10 days of diloxanide. All patients should be reassessed two to three months after treatment, to ensure that the parasite has been cleared and that there is no chronic carrier state with continued cyst excretion.

3.5. Balantidium Coli

B. coli is a large, ciliated protozoan that uncommonly causes an illness similar to amebic dysentery. B. coli is usually easy to identify in stool samples, owing to its large size. It is acquired in tropical or subtropical countries from exposure to pigs, which frequently carry this organism without signs of illness. Treatment is with tetracycline 500 mg q.i.d. for 10 days. B. coli is also sensitive to ampicillin and metronidazole.

3.6. Blastocystis Hominis

B. hominis is an anaerobic protozoan which is frequently found in asymptomatic individuals, B. hominis may be a cause of diarrhea in some patients found to have large numbers of this protozoan in the stool. Treatment is with either metronidazole 750 mg t.i.d. for 10 days or high dose trimethoprim/sulfamethoxazole.

3.7. Dientamoeba Fragilis

Dientamoeba Fragilis is also a protozoan related to Trichomonads, it is a human pathogen. D. fragilis commonly causes abdominal pain, diarrhea, bloating and other vague abdominal symptoms. This parasite should be ruled out in individuals who are suspected of having diarrhea predominant IBS, or of microscopic colits (see below). Co-infection with *B. hominis* appears to be a common finding in some labs where parasite stool studies are still done by microscopy. If D. fragilis is identified, treatment has been associated with rapid clearing of symptoms. Treatment is with iodoquinol 650 mg TID for 20 days, doxycycline 100 mg BID for 10 days, or metronidazole 500 mg TID for 10 days.

4. Intestinal Nematode Infections

4.1. Roundworm (Ascaris Lumbricoides)

Roundworm or ascaris, one of the more common nematodes found in humans, is most often found in the tropics. Usually eggs are ingested from contaminated foods or dirty hands. The eggs hatch in the intestine and spread by the blood to the liver and then to the lungs. An eosinophilic pneumonitis develops the larvae migrate through the alveoli, up the trachea, through the larynx, where they are swallowed. Roundworms develop into adult worms in the small intestine. The adult worms can cause intestinal obstruction symptoms if large numbers are present, and can cause biliary symptoms if they migrate into the common bile duct.

4.2. Hookworm (Ancylostoma Duodenale;
Necator Americanus)

Hookworm is a nematode which can infiltrate the skin from contaminated earth, found in areas with fecal contamination of the soil. A pruritic rash develops at the site of the hookworm entry into the body. The filarial larvae then travel to the lungs, migrate through the alveoli, up the trachea, through the larynx, where they are swallowed. After being swallowed, they cause nausea, diarrhea, vomiting, abdominal pain and flatulence. Many patients present with iron deficiency from a daily blood loss of 0.1–0.4 mL with each worm.

4.3. Whipworm (Trichuris Trichiura)

Whipworm can also cause iron deficiency if large numbers infect the GI tract. It primarily invades the colon. Bloody diarrhea develops with larger infestations. It is easily diagnosed by stool analysis looking for the typical eggs, but is increasingly diagnosed at colonoscopy during investigation of the bloody diarrhea, where the worms are easily seen if present.

4.4. Pinworm (Enterobius Vermicularis)

Pinworm is probably the commonest nematode worldwide. It usually causes

pruritus ani, often worse at night when the worms migrate onto the perianal skin and lay their eggs. Pinworm is probably the most common nematode encountered in Canada, especially in children. Diagnosis is by identification of the eggs from the perianal skin, usually collected in the early morning before defecation.

4.5. Strongyloides Stercoralis (Strongyloidiasis)

Strongyloides stercoralis is widely found in the tropics. It is the only nematode that can multiply and reproduce its entire life cycle within the human host. This causes persistent reinfection over many years after the original infection. Larvae can penetrate intact skin or the eggs can be ingested. Filariform larvae that penetrate the skin travel hematogenously to the lungs and then, as with the other worms, travel into the airways, into the larynx, and are swallowed. In the intestine the larvae become adult worms. When the eggs are ingested, they become filariform larvae in the intestine; then the larvae invade the blood vessels, thus reinfecting the host.

Symptoms of strongyloidiasis vary and may include abdominal pain, diarrhea, nausea and vomiting. With mostly intestinal involvement of strongyloids diarrhea develops. In children, a syndrome similar to celiac disease with protein-losing enteropathy can develop. The majority of adult infections are asymptomatic, or are only intermittently symptomatic. Recurrent urticaria can develop where the worms infiltrate the skin, particularly the perianal skin and gluteal areas.

Diagnosis can be confirmed by stool analysis but can be falsely negative in up to 25% of cases, even after repeated stool analysis. The larvae look similar to hookworm. An ELISA test is useful for diagnosis, but there may be overlap with the presence of Filaria species. Eosinophilia is often present, even in asymptomatic individuals.
Thiabendazole is usually used to treat strongyloids, 25 mg/kg twice daily to a maximum of 3 g daily for two days, or for five days for disseminated disease. Albendazole or ivermectin may be used if the patient is unable to tolerate thiabendazole, but these drugs appear to be less effective than is thiabendiazole against S. stercoralis.

With the hyperinfection syndrome, when large numbers of the worms are present (often in association with immune suppression, as with steroid therapy), antibiotics are often needed to treat the septicemia that results if the intestinal damage allows secondary bacterial invasion.

5. Sexually Transmitted Diseases of the Anorectum

There is an increasing incidence of venereal infections of the anorectal region, mainly accounted for by sexual practices among gay men. Many of these diseases may mimic nonvenereal conditions of the anorectum, and multiple venereal infections may coexist. While immunocompetent gay men are subject to infection with the usual venereal pathogens, HIV/AIDS patients may additionally suffer from opportunistic infections of the gut.

The common anorectal venereal infections seen in North America are discussed here.

Condylomata acuminata, or venereal warts, are seen in the perianal region and anal canal, as well as the vulva, vagina and penis. They are most often seen in men who have sex with men (MSM). The causative agent is believed to be a papilloma virus, which has an incubation period of one to six months. Symptoms are generally minor – itching, and occasionally bleeding. Perianal warts are frequently accompanied by warts within the anal canal, and these must be looked for at anoscopy. Many treatments exist. None has a better than 70% chance of eradicating the disease by a single application. For perianal and anal canal warts, electrocoagulation or laser destruction is preferred. For extensive and persistent disease, immunotherapy with an autologous vaccine may be successful. Squamous cancer has been seen to arise in condylomata acuminata.

Neisseria gonorrhoeae may produce proctitis. The incubation period of gonococcal proctitis is 5 to 7 days. Gonococcal proctitis is most often asymptomatic. Symptoms may include mucopurulent discharge and tenesmus. Proctoscopy reveals a thick, purulent discharge on a background of mild, nonulcerative inflammation of the distal rectum. Gram's stain is unreliable, but culture of the pus confirms the diagnosis.

Serologic testing for syphilis should be carried out. Treatment for MSM is ceftriaxone, 250 mg IM once. *Syphilis* can affect the anal region. The incubation period ranges from 9 to 90 days. The primary lesion is a painful chancre, which may be mistaken for a fissure. However, chancres are off the midline, are often multiple, and have an atypical appearance. Bilateral inguinal lymphadenopathy may be present. The chancre regresses over 6 weeks. *Treponema pallidum* is demonstrated from the primary lesion by darkfield microscopy. Serologic testing will be positive within a few weeks of the appearance of the chancre. If untreated, the secondary stage of syphilis may involve the anal area 6 to 8 weeks after healing of the chancre. This takes the form of a rash or of condylomata lata – flat, wart-like lesions teeming with *Treponema pallidum*. Treatment of primary and secondary syphilis is with benzathine penicillin G, 2.4 million units IM given once. Sexual contacts should be treated prophylactically.

Herpes simplex 2 may infect the anorectum. The incubation period is 4 to 21 days. Constitutional symptoms are followed by severe anorectal pain. Small vesicles and aphthous ulcers are seen perianally, as well as in the anal canal and lower rectum. There may be tender inguinal lymphadenopathy. Viral cultures of the vesicular fluid will be positive for herpes simplex 2 and rectal biopsy has a characteristic appearance. Spontaneous resolution occurs over several weeks. Recurrences are frequent but less severe.

Immunosuppressed patients may develop a severe, destructive process. Treatment is with tub baths and analgesics. Topical acyclovir q8h for 5 days shortens the symptomatic period and the duration of viral shedding. However, oral antiviral therapy is the preferred method of treatment, as it decreases the severity of symptoms and will also decrease the disease duration. Acyclovir is given as 400 mg TID or 200 mg five times a day. Famciclovir 250 mg TID or valacyclovir 1,000 mg BID are equivalent in efficacy, but are more expensive than acyclovir. Intravenous acyclovir is used when there is proctitis in addition to anal and perianal disease. In the HIV/AIDS patient, acyclovir is used intravenously in the acute phase, followed by oral acyclovir for 6 months.

Chlamydia proctitis with non-LGV (lymphogranuloma venereum) serotypes is almost identical to gonococcal proctitis. However, the LGV serotypes are invasive and produce a severe proctocolitis with pain, tenesmus, discharge and diarrhea. Chlamydia is isolated from the rectum. Treatment is with doxycycline 100 mg po BID for 7 days, or azithromycin 1 g po as a single dose.

6. Lower Gastrointestinal Bleeding / S.J. Vanner

Lower GI bleeding often presents as a medical emergency. Like other medical emergencies, optimum patient care requires careful assessment and resuscitation. The history and physical findings provide important clues to the etiology of lower GI bleeding, and are critical for determining the severity and location of the bleeding site.

Lower GI bleeding can be classified arbitrarily as major or minor. Patients presenting with the passage of significant amounts of bright red blood per rectum (BRBPR), together with hemodynamic compromise have major GI blood loss and are at risk of life-threatening hypovolemia. Be wary of the patient who may have stabilized temporarily or received

intravenous fluids prior to a full clinical assessment. Historical clues to a major bleed include the occurrence of syncope or presyncope prior to the person seeking medical care. The vital signs, with particular
attention paid to postural changes, are crucial to assessing severity. The passage of bright red blood per rectum usually originates from the colon. However, it is important to remember that brisk bleeding from a site in the upper GI tract may masquerade as a major lower GI bleed.

In contrast to the patient with major lower GI bleeding is the person who describes the passage of bright red blood per rectum as blood on the tissue paper or on the outside of formed stool in the absence of other symptoms. Such patients, whose general physical examination is normal, usually have a minor lower GI bleed. Most often this is due to local perianal pathology, but distal colon pathology should always be ruled out.

7. Determining the Site of Bleeding (Upper or Lower GI Tract)

In the clinical setting of a major lower GI bleed with the passage of bright red blood per rectum and hemodynamic compromise, there are a number of important clues that may raise the suspicion of an upper GI source. These include a past history or symptoms of peptic ulcer disease, NSAID/ASA use, prior abdominal aneurysm repair, alcohol abuse and coexisting liver disease. Unfortunately, the lack of upper GI symptoms does not exclude peptic ulcer disease, as a number of peptic ulcers present as major GI bleeds without a previous typical ulcer history. These painless bleeding gastric or duodenal ulcers are particularily common in persons whose peptic ulcer is associated with the use of aspirin (ASA) or nonsteroidal anti-inflammatory drugs (NSAIDS).

On physical examination, the finding of hypovolemic shock, particularly in a young person, should trigger immediate consideration of a proximal source of bleeding. Features of chronic liver disease and portal hypertension suggest esophageal or gastric varices as a possible cause. Most major upper GI bleeding, even in a young person, is accompanied by a transient rise in the BUN (blood urea nitrogen), whereas this is not typical in a lower GI bleed unless there is renal comorbidity.

When an upper GI source is considered, a nasogastric (NG) tube is placed. A nasogastric tube returning bloody gastric aspirate positively identifies a proximal source of bleeding. A negative aspirate will exclude significant bleeding from the esophagus or stomach but may fail to identify bleeding from the duodenum. Even aspirates with bile staining and no blood may fail to identify 5−10% of bleeding duodenal ulcers.
When an upper GI source cannot be excluded with confidence, urgent upper endoscopy is required.

Another potentially confusing scenario involves the patient presenting with melena. Melena results from the digestion of blood as it travels through the GI tract, and usually originates from the upper GI tract. However, occasionally the transit of blood from a bleeding right colon source is sufficiently slow that stool can appear as melena or melena mixed with dark red blood.

Positive fecal occult blood tests (FOBT) are another clue to gastrointestinal bleeding. Testing should be done with patients on a controlled diet (no red meat, vitamin C or aspirin) to minimize a falsely positive FOBT.

8. Major Lower GI Bleeding

Angiodysplasia and diverticular bleeding are the two most common causes of major lower GI bleeding, accounting for up to 70% of cases. Angiodysplastic lesions result from dilation and tortuosity of submucosal veins associated with small arteriovenous communication with submucosal arterioles. These lesions are typically multiple, less than 5 mm in diameter, and are most commonly found in the right colon and cecum. The pathogenesis of these lesions is unknown. They occur most commonly in elderly patients, and differ from congenital vascular lesions. Diverticula are located predominantly in the left colon, but diverticulae in the right colon bleed more frequently. The pathophysiology underlying diverticular bleeding is uncertain, but may result from rupture of arteries that penetrate the dome of the diverticulum.

A number of other possible but less common causes exist for lower GI bleeding (Table 2). Many of these more typically present with minor lower GI bleeding and a clinical picture dominated by other features such as diarrhea and anemia. Angiodysplasia, unlike diverticular bleeding, can also present with minor chronic GI bleeding, and may even present as chronic iron-deficiency anemia secondary to microscopic blood loss. In contrast to angiodysplasia and diverticular bleeding, which are relatively painless, bleeding secondary to colonic ischemia is typically preceded by minutes to hours of severe abdominal pain. Abdominal x-rays may demonstrate dilation of the bowel, thickening of the bowel wall, and "thumb-printing" (edema of the bowel wall). Thumb-printing is neither specific nor sensitive.

Table 2. Causes of major lower GI bleed

➢ Very common
  o Diverticular disease
  o Angiodysplasia

➢ Less common
  o Ischemia
  o Neoplasia
  o Inflammatory bowel disease
  o Hemobilia
  o Perianal disease
  o Aortoenteric fistula
  o Solitary rectal ulcer

Most major lower GI bleeding will stop without intervention and can be investigated electively, but up to 25% will continue to bleed and require immediate investigation and treatment. After resuscitation, the next priority is to identify the site of bleeding. Radionuclide scanning using technetium-labeled red blood cells is least invasive and readily available in most centers, but interpretation is fraught with false negative and positive results. Although angiography is less available and more invasive, it is more accurate and has the advantage of

therapeutic intervention with embolization of the arteriole feeding the bleeding lesion. Colonoscopy can also be attempted to identify the bleeding lesion, and if angiodysplasia is evident it can be treated with electrocautery. However, unless the rate of bleeding is relatively slow, ongoing bleeding usually obscures the lumen, making it difficult to identify the responsible lesion and technically difficult to advance the colonoscope to the site of bleeding. In some cases, continuing bleeding (requiring transfusions of 6–10 units of blood) requires either urgent angiography with embolization or surgical resection with a subtotal colectomy.

9. Minor Lower GI Bleeding

Minor bleeding from the lower GI tract is a common complaint and requires a careful approach to differentiate minor pathology such as hemorrhoids and fissures from serious problems such as colonic tumors. Patients may notice blood only on the outside of formed stool or on the tissue paper. This suggests that the blood originates from the anal canal or the rectosigmoid region. Alternatively, some patients notice that the blood is mixed in the stool, suggesting that bleeding is more proximal within the colon.

Hemorrhoids are the commonest cause of minor bleeding (Table 3). Even when the history is very suggestive for hemorrhoids, endoscope assessment should be carried out to ensure that a rectal lesion such as proctitis or a tumor is not mimicking this presentation. Patients with ulcerative proctitis often have frequent bowel movements, but may pass only bright red blood and mucus. Radiation proctitis can present shortly after radiotherapy treatment, but is often delayed by many months or years. This condition results from chronic inflammation within the blood vessels, called endarteritis obliterans, and this indolent process underlies the delayed presentation.

Table 3. Causes of minor lower GI bleed

- Very common
  - Hemorrhoids
  - Fissures
  - Other perianal disease
  - Proctitis

- Less common
  - Neoplasia
  - Inflammatory bowel disease
  - Infectious colitis
  - Radiation colitis
  - Angiodysplasia
  - Ischemia
  - Rectal ulcer
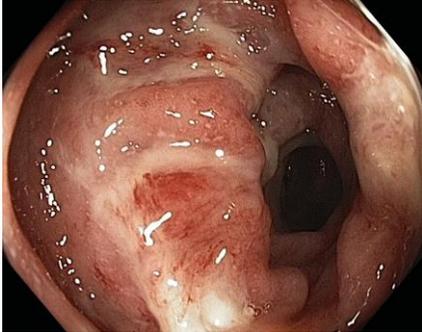
Figure 4. Endoscopic appearance of colitis. Note the diffuse reddening of the mucosa, which will bleed if touched. This patient had moderately active ulcerative colitis, but infection and other causes of colitis (eg. Ischemia) can look identical. Contrast this image with the image of ischemic colitis at the splenic flexure in Figure 2.

Chapter 12: Ulcerative Colitis and Other Conditions that cause Colitis-like Symptoms
G.K. Turnbull

1. Introduction

Ulcerative colitis (UC) along with Crohn disease are the two major inflammatory bowel diseases that affect the colon. The cause of UC is unknown, but it appears to have a genetic association with it being much more common if an individual has a relative with the disease. About 15% of UC cases have a genetic history of another relative with UC. The disease most commonly affects young adults before the age of 30, but can start in young children or in older adults. The incidence of UC has been fairly stable over the past 50 years, as compared with Crohn disease, which has had a significant increase in both incidence and prevalence.

Most patients with UC present with sudden onset of diarrhea with blood. The severity of symptoms can be quite variable. Sometimes the initial symptoms can be mild and the patient has some bleeding that then gradually clears, only to come back usually with more symptoms at a later date. Abdominal pain may also be present, but is usually mild in UC, and is mostly described as cramping pain associated with the bloody diarrhea. The disease can present with a severe exacerabation but this only occurs for the first presentation of UC in about 5% of cases. Sometimes, the patient has had mild episodes of rectal bleeding that clear, and then has a severe attack before UC is diagnosed. The disease can affect variable lengths of the colon, from just the rectum to the entire colon (pancolitis). The extent of the colon affected will often dictate how the patient presents. With more colon involved, there is more cramping with bloody diarrhea. The more severe attacks of UC are usually in persons with pancolitis. Patients who have just the rectum involved may even present with constipation, due to the inflamed rectum making it difficult for the formed stool from the proximal colon to be expelled.

The diagnosis of UC is confirmed by doing endoscopy and biopsy of the colon. Infectious causes need to be ruled out, as bacterial infections may mimic UC. After the diagnosis of UC has been made, the disease is prone to repeated flare-ups. To reduce the frequency and severity of the recurrent attacks of UC, life-long medication is usually required to control the disease ("maintenance therapy"). When the disease flares, it is important to repeat the stool cultures, especially for *C. difficile,* because this may cause flare-ups of UC without the patient previously having taken antibiotics.

1.1 Therapy

Treatment consists of oral and/or rectal 5-ASA based therapy (mesalamine or sulfasalazine) as first line therapy, for mild to moderate attacks ("flare-ups") of UC, then increasing therapy ("stepping up") depending on the response to 5-ASA therapy. The patient is usually started on 5-ASA because there are fewer side-effects with these medications and they have the additional benefit of helping to keep the disease in remission once a flare has occurred.

Sulfasalazine is usually dosed between 4 to 6 grams per day in split doses. It has frequent side-effects and for this reason, mesalamine was developed (it is the active ingredient in sulfasalazine) to try to minimize these side-effects. The dose of mesalamine is 4 to 4.8 grams per day, again in divided doses. Different coatings have been developed to deliver the 5-ASA to the colon. One coating, called MMX, allows the patient to take all their pills once a day in order to facilitate their compliance with the medication. Compliance is especially important for maintenance therapy to prevent UC flare-ups. When the sufferer has distal disease in the rectum or rectosigmoid, 5-ASA or steroid containing enemas may be useful, either on their own or together with an oral preparation.

LEARNING POINTS:
- o Ulcerative colitis and Crohn disease are common in Canada (3 per 1000 persons)
- o The diagnosis is suspected from symptoms such as pain and bloody diarrhea, and is confirmed by characteristic changes on diagnostic imaging, and endoscopy with mucosal biopsies
- o Most patients respond to 5-ASA compounds, which must be used long-term to reduce the frequency and severity of recurrent attacks
- o Because an infection with c.difficile may cause an attack of UC, always culture the stools of a UC patient with recurrent symptoms
- o The risk of CRC is increased in persons with UC for more than 10 years, and frequent colonoscopic surveillance is necessary

Predisone is usually only used to control severe flare-ups of the UC and is used in oral doses of 40 to 60 mg/day, usually dosed once or twice a day (ie. 20mg PO bid). Although prednisone and other steroids are very effective in settling flares of UC, the goal of therapy should be to minimize the patient's exposure to steroid therapy, so that 5-ASA maintenance therapy controls UC activity. Prednisone should be tapered once the symptoms of the severe attack are abating, but unlike other illnesses where prednisone is used, the taper has to be gradual, usually only 5 mg per week (sometimes even more slowly) until the prednisone can be stopped. Steroids must never be used for maintenance therapy. Immunosuppressive therapy (see below) should be considered in a patient if there has been more than one UC flare in a year, which has be sufficiently severe to require steroid therapy.

The long-term complications of steroids mandate that patients with UC be on steroids as infrequently as possible and tapered off this drug once their disease flare has settled. During severe exacerbations of the disease, the patient is admitted to hospital, and IV steroids are usually used to maximize therapy and control the inflammation (bioavailability of steroid is much higher with IV than PO/PRN dosing). With severe attacks of colitis, the IV steroid is usually used for 48 to 72 hours at high dose (ie. Solumedrol 40mg bid) and the inflammation should be showing signs of improving. If the patient does not quickly improve, then alternate therapies should be considered, such as IV cyclosporine, IV/SC anti-TNF therapy, or colectomy. When the patient has a severe UC attack, they need daily examination of the abdomen, as well as abdominal views to ensure they are not developing megacolon, which is an indication for urgent colectomy.

During severe attacks, medications that can decrease intestinal contractility need to be stopped (ie) loperamide, anti-cholinergic medications, anti-spasm medications and the opiate doses used for pain control need to be minimized. Anti-motility drugs all tend to worsen the colonic inflammation, and toxic megacolon may result, an indication for urgent colectomy.

When patients have repeated attacks of colitis and the 5-ASA therapy is not controlling their colitis and preventing flares, then therapy with an immunosuppressive drug should be considered. Imuran (azathioprine) or 6-mercaptopurine are the usual agents used to try to settle the disease flares. There is only minimal data on the use of methotrexate in UC. Immunosuppression may work best if started with steroid therapy and then the steroid tapered gradually once the Imuran has been started. These immunosuppressive agents have a slow onset of action (2-3 months). Imuran and 6-mercaptopurine are essentially the same drug, so reactions to one drug may occur with the other. Imuran is dosed at 2.5 mg/kg/day and 6-mercaptopurine is dosed at 1.5 mg/kg/day. They can cause bone marrow suppression and liver inflammation

(hepatitis), so regular blood testing (CBC, alkaline, phosphatase, ALT) is needed if these drugs are to be used in order to identify if these complications are developing. If the WBC falls below 4, or if the liver enzymes become abnormal, the immune suppression will usually need to be stopped, or the dose reduced. Some patients may develop a drug fever with the drug, or can have drug-induced pancreatitis. If pancreatitis develops, the patient should not be given Imuran or 6-mercaptopurine again, because this is a type of allergic response to the drug and subsequent therapy with Imuran will lead to more severe and potentially fatal attacks of pancreatitis. Patients with UC needing immunosuppressive therapy should be followed by a specialist physician familiar with the complications of these drugs.

In the acute setting of a severe flare-up of UC, the patient may not respond to high dose steroid therapy and surgery is sometimes necessary to prevent perforation of the colon. Perforations have a high risk of mortality. After 48 to 72 hours of high dose steroids, the need for possible surgery should be considered. This drug infliximab can settle the UC flare under these circumstances and although it may not, many patients will opt for this therapy rather than undergo a colectomy. The dosage of infliximab is usually 5 mg/kg/dose given at 0, 2, and 6 weeks then given every 8 weeks after this. Again, specialist therapy is required in making this decision if infliximab therapy is needed for a patient not responding to steroid therapy. Patients should be transferred to a hospital with experienced surgeons who are familiar with colon surgery if a patient develops severe colitis and requires hospitalization and should be done early in the flare-up to facilitate a favourable outcome. If the patient does not respond to high dose IV steroids, or is unresponsive to infliximab, then surgery should be done if there is no response to avoid the patient having a colonic perforation due to severe colonic inflammation.

Surgery for UC requires the colon and rectum to be removed, so that no colonic mucosa remains to be inflamed. This is now done in a two stage operation where the colon is resected, usually leaving the rectum intact and an ileostomy created. Once the inflammation has been allowed to settle for a number of months and the patient recover from the severe inflammation, the next stage of the surgery is done.

Many patients now opt for a pelvic pouch created from the end of the ileum and anastomosed to the anus after the rectum is resected, preserving the anal sphincters. After the ileoanal pouch anastomosis had a chance to heal then the ileostomy is closed. This operation affords the patient the ability to still pass stool per anus without requiring a permanent ileostomy after total colectomy. This is a very challenging operation to do well and should only be done in centers where the surgeons specialize in colorectal surgery, to afford the patient the best chance of a good result. The main problem of this surgery is in young women who have not yet had children as there is a high rate of infertility after this operation, presumably due to the extensive pelvic manipulation required for this operation.

2. Irritable Bowel Syndrome

Persons exhibiting symptoms from the lower GI tract are often suffering from the irritable bowel syndrome (IBS). The cause of IBS is largely unknown, but does sometimes occur after an episode of infectious diarrhea. IBS patients have no identifiable organic disease of the gastrointestinal tract, yet they experience frequent symptoms from the bowel. Large epidemiologic studies suggest that IBS occurs in at least 15% of the population. The commonest symptom that brings a patient to a doctor is abdominal pain. A positive diagnosis can be made, particularly in women, if the abdominal pain is present for at least three months in the last year, and if the pain is relieved by defecation. The abdominal pain is also associated with a change in

stool consistency and stool frequency. These criteria are termed the Rome III criteria that have been shown to be reliable in making a positive diagnosis of IBS.

The following criteria are also used to help confirm a positive diagnosis. The more of these symptoms that are present, the more likely the diagnosis is irritable bowel. These symptoms are: abdominal bloating or distension, mucus in the stool, and difficult defecation. Patients who have difficulty with defecation may complain of "urgency," with the sudden urge to pass stool and a fear of incontinence if defecation is not performed immediately. Many patients with this symptom will relate that they always identify where the toilet is when they are away from home.

The fear of incontinence can often greatly limit a patient's ability to function normally in society. Other patients with difficult defecation may have to strain – defined as having to hold their breath and push when attempting defecation. Straining is defined as "constipation" when a patient must strain 25% or more of the time when trying to defecate. Finally, some patients describe a feeling of incomplete emptying after passing stool. This symptom has to be asked for specifically, as most patients will not spontaneously report it. Nevertheless, the symptom is commonly reported by patients with an irritable bowel.

The presence of mucus in the stool can be alarming to some patients, since they may interpret this to mean they have "colitis." In the past, some doctors used to refer to irritable bowel as "mucus colitis," which is a misnomer since there is no "colitis" or inflammation of the colon in irritable bowel. Mucus is a normal product of the colon, and only if mucus and blood are seen together should other diagnoses such as "colitis" be considered. The typical stool pattern described by patients with IBS is the change in stool character and frequency with the onset of abdominal pain.

Typically, patients will pass a normally formed stool (sometimes even a constipated stool) first thing in the morning. Then, with the attacks of abdominal pain, the stools become more frequent and looser, sometimes becoming liquid. Once bowel movements cease the pain is relieved, but the pain may recur again later in the day, often precipitated by eating high-fat foods or other gut stimulants (e.g., coffee). The vast majority of people with IBS have their symptoms begin in young adult life. One should consider other colonic diseases in patients over the age of 40 who develop these symptoms for the first time. Sometimes later in life patients can develop irritable bowel after severe infectious diarrhea, but in this population as well, further investigations are warranted to ensure no other cause for the change in bowel function.

Those constipated patients who have infrequent stool alternating with occasional diarrheal stool have the most common presentation of irritable bowel syndrome. Yet there are a great many patients, almost all female, who have infrequent stool passage, and this group must be considered as separate from the usual irritable bowel syndrome patent for they may be among those rare patients with a secondary cause of constipation. IBS is a disorder affecting the entire gut, and these patients frequently have symptoms from other parts of the GI tract besides the colon, as well as from other organs. Upper GI symptoms are common in IBS; these include heartburn and dyspepsia. Dyspepsia symptoms in general occur more commonly than lower bowel symptoms, but may be due to many other causes, including reflux esophagitis, gastritis, peptic ulcer disease and, less commonly, biliary tract and pancreatic disease. When upper GI symptoms are associated with IBS, other underlying diseases must be considered.

Other associated symptoms include frequent headaches and urinary symptoms that are similar to bowel symptoms, in that patients can have urgency and frequency of urination. These symptoms are often worse at times when the bowel symptoms are troublesome. In women,

irritable bowel symptoms can often be exacerbated or worsened around the time of menstruation. Indeed, bowel symptoms associated with menstruation occur in at least 50% of the normal female population.

When assessing a patient complaining of irritable bowel symptoms, remember that only a small proportion of patients with an irritable bowel present to doctors with these symptoms. Patients who consult a physician about their IBS symptoms often have psychological problems, with increased levels of distress and depression. It is important to inquire about these problems, as successful treatment often consists of dealing with the distress and/or depression that exacerbates the irritable bowel symptoms. These mental health symptoms may often be the reason that the patient has sought medical attention in the first place.

LEARNING POINTS:
-In young persons with recurrent abdominal pain associated with an altered bowel habit, and no alarm symptoms such as bleeding or weight loss, suspect IBS
-While a positive diagnosis of IBS may be made, most physicians are more comfortable performing blood and stool tests to exclude possible intestinal infection or inflammation
-The treatment of IBS is the care of the patient, as well as symptomatic management of symptoms

2.1. Differential Diagnosis

The altered bowel habits in persons with IBS include diarrhea (D), constipation, and diarrhea alternating with constipation (D/C). In the person suspected of having D-IBS, or D/C-IBS, consider other possibilities such as lactose intolerance, celiac disease, bile salt wastage, small intestinal bacterial overgrowth, or giardiasis (See Chapter 6: The small intestine).

All patients should have a thorough physical examination, looking for evidence of disease in other organ systems such as the thyroid, which can present with a change in bowel habit. Patients with an irritable bowel will often have tenderness over the colon, particularly the sigmoid colon, on palpation. The identification of an enlarged liver or spleen or other abdominal masses necessitates further investigations for alternate diagnosis. A barium enema is rarely required in a young healthy adult with new onset of IBS symptoms. However, a patient over the age of 40 presenting with new onset IBS symptoms warrants at least a barium enema and a sigmoidoscopic examination. The barium enema should also evaluate the terminal ileum if there is pain on palpation in the right lower quadrant. A complete blood count with platelet count should be done, as an elevated platelet count is often a sensitive finding for underlying inflammation and in the presence of bowel symptoms could mean the presence of early inflammatory bowel disease. Crohn disease is more likely to present this way than irritable bowel.

The persistence of the abdominal pain, even though lessened after bowel movements, would suggest possible underlying inflammation of the gut rather than an irritable bowel. Ulcerative colitis usually presents with rectal bleeding. Rectal bleeding is not a symptom of irritable bowel and its cause must always be investigated. Fever, weight loss and symptoms that wake a patient from sleep, as opposed to early waking in the morning, are all symptoms that should be further investigated.

The presence of nocturnal symptoms, particularly with diarrhea waking the patient at night, is rarely due to an IBS. Occasionally patients with depression who have early morning waking report nighttime diarrhea, but in general further investigations are indicated.

2.2. Therapy

The therapeutic approach in IBS is as much reassurance as any specific therapies, as most patients do not have any "disease." It is most important to do a thorough history and physical examination to ensure that the complaints are not due to any underlying disease. Once this has been confirmed, explain to the patient how the bowel can produce these symptoms and that there is no cause for concern. Since patients presenting with IBS symptoms frequently have more distress and tend to be more prone to seek medical attention for other minor medical conditions than other patients (so- called "illness behavior"), these patients may require considerable reassurance to convince them that they do not have serious disease. Part of this reassurance will be provided by screening blood tests such as a complete blood count with platelet count.

Sigmoidoscopic/colonoscopic examination will rule out most underlying early inflammatory bowel disease and any rectal pathology, particularly in patients complaining of defecation difficulties or a sensation of being unable to empty the rectum adequately. If diarrhea is present, the stool should be analyzed for pathogens.

Following these initial screening tests emphasis should be placed on the stresses present in the patient's life, which may trigger their bowel complaints. Evaluating the level of stress and taking steps to correct it will often be helpful. Many patients, particularly those who have symptoms of constipation, may be helped with a high-fiber diet (see Section 9, Chapter 10).

Drug therapy for irritable bowel is usually empiric, directed at the most troublesome symptom (ie. Pain, bloating, diarrhea, constipation). There is no single drug that treats all the varied symptoms in irritable bowel. Occasional patients will continue to have intractable symptomatology. In this situation selected medications for specific symptoms may be helpful. Table 5 outlines some drugs that may be useful for specific symptoms. Drug therapy for IBS should always be restricted to short periods during exacerbation of symptoms, and patients should be taken off medications when they are well. As irritable bowel is a chronic condition and is probably "normal" for these patients, the chronic use of medications often reinforces the notion that they have a "disease." Reassuring the patient that there is no association between irritable bowel symptoms and the development of more serious bowel disease such as colon cancer or inflammatory bowel disease can often alleviate some of the unreasonable yet very real concerns of many patients who present to doctors with these symptoms.

3. Microscopic Colitis

This condition has been recognized increasingly in which the patient with microscopic colitis presents with painless diarrhea. The colon appears normal on both radiologic and colonoscopic examination. The diagnosis is made from biopsies of the normal appearing colon. There are two types of microscopic colitis, "lymphocytic colitis" and "collagenous colitis." On histological examination there is an increase in the inflammatory infiltrate of the lamina propria. In collagenous colitis, the basement membrane of the colonic mucosa is thickened by a band of collagen, and in lymphocytic colitis there is an increase in lymphocytes. The natural history of these diseases is unclear and no infective agent has been found. In most patients the disease appears to follow a benign course, but about half of patients continue to have significant diarrhea for more than two years.

The symptoms of microscopic colitis are usually controlled by antimotility agents such as loperamide, by use of 5-aminosalicylic acid–based therapies directed at the colon or oral budesonide enteric coated tablets. The most recent studies of therapy have found budesonide (Entocort) to be the most effective therapy. Cholestyramine 4 grams four times a day has also

had reports of success in this condition. Glucocorticoids also control the diarrhea, but in view of the usually benign course of this illness in most patients, steroid therapy should be used only in severely symptomatic patients who cannot be controlled by other therapy.

4. Eosinophilic Colitis

Eosinophilic gastroenteritis is an uncommon inflammatory condition that affects primarily the upper GI tract and small intestine (see Chapters 4, 5 and 6).

A separate condition, called "eosinophilic colitis" in which patients with connective tissue disease present with diarrhea of uncertain cause, with negative stool investigations.

Like microscopic colitis, the mucosa looks normal on colonoscopy, and the diagnosis is made on mucosal biopsy. The mucosal biopsy shows increased eosinophils in the lamina

propria. All patients initially respond to steroids, but not all patients resolve over time, and some may need prolonged steroid therapy. Because of its lower systemic toxicity, the use of budesonide (as with microscopic colitis) may be the best first line therapy for this rare condition.

Chapter 13: Colonic Neoplasia *G.K. Turnbull, M. Burnstein, J.A. Rowe and S.J. Vanner*

1. Introduction

Colorectal cancer (CRC) is the second most common cancer (after lung cancer) in men and women combined in Canada . Unlike lung cancer, CRC has a high survival rate in patients diagnosed before it has spread beyond the confines of the bowel wall. Since CRC is a very common cancer, has a high survival rate with early curative surgery and is poorly responsive to other forms of cancer therapy, a high index of suspicion must be maintained in approaching patients with symptoms of colonic dysfunction (Table 1), especially if they are over the age of 40, when the incidence of CRC begins to rise. Increased CRC risk is also seen in patients with ulcerative colitis or Crohn's colitis, a history of uterine or ovarian cancer, or a family history of CRC or colonic adenomas (including familial polyposis syndromes).

The tumor, node, and metastasis (TNM) staging system has largely replaced the older Dukes' classification for staging CRC after surgical resection. Table 2 details the TNM staging system for CRC and compares it to the older Dukes' A to D classification. Other factors that increase the mortality from CRC besides the stage of the tumor, are poorly differentiated histology and vascular histological invasion by the tumor at the time of resection. Other poor prognostic indicators for CRC are cancers that have perforated, are adherent to adjacent organs and colon cancer presenting with complete bowel obstruction. Early recognition is of the utmost importance to try to identify CRC at an early, curative stage. Therefore, patients with intermittent symptoms are as important to investigate as patients with persistent symptoms, and the story of occasional blood in the stool in a patient over 40 years of age should not be attributed to local anorectal disease without first excluding a more proximal lesion.

Table 1. Presenting features of colon cancer

- o   Abdominal pain, including symptoms of bowel obstruction
- o   Change in bowel habit
- o   Abdominal complaints of recent onset
- o   Rectal bleeding or melena stool
- o   Abdominal mass
- o   Iron deficiency anemia
- o   Hypokalemia

Table 2. Colorectal adenocarcinoma staging

TNM stage Dukes' stage Tumor invasion 5 year survival

T0N0M0   N/A Mucosa only 100%
T1N0M0   A Submucosa 90–95%

No lymph nodes or distant metastases
T2N0M0 B1   Muscularis involved 85%
No lymph nodes or distant metastases
T3-4N0M0 B2   Tumor to serosa (T3) or through 70–75%

serosa (T4)
No lymph nodes or distant metastases
T2N1M0 C1   Muscularis involved but not to serosa 35–65%

Lymph nodes involved
T3-4N1M0 C2   Tumor to serosa (see T3/4 above) 35–65%
Lymph nodes involved

TxNxM1   Distant metastases (liver) regardless <5%

Many patients with CRC may present with no gastrointestinal symptoms, but rather with an iron deficiency anemia due to chronic bleeding from the tumor. Patients may not see blood in the stool or note a melena stool, particularly when there is a right-sided colonic lesion. A change in bowel habit, often with constipation alternating with diarrhea, may be the first sign of obstructive symptoms from a CRC, and should never be ignored in a patient over 40 years of age with a recent onset of these symptoms. Some patients may present with primarily diarrhea if they have a high output of mucus and fluid from the tumor; in this instance the tumor is often sessile in appearance (see below) and large, with the histology of a villous adenoma. Some patients may have hypokalemia due to the large amounts of mucus secretion from the tumor.

Carcinoembryonic antigen (CEA) is a tumor marker that has limited use in diagnosing CRC but is often useful in following patients with CRC. A high CEA level before surgery often suggests a poor prognosis with probable metastases. A CEA level that does not fall to normal levels one month after surgery suggests that all the cancer has not been resected. After surgery, if the CEA falls, then regular monitoring of CEA levels may be useful to identify patients with early cancer recurrence. Sometimes a search for metastases will reveal a solitary lesion in the liver that may be surgically resectable, or with the early use of chemotherapy, may lead to a cure of the cancer.

2. Polyp–Carcinoma Sequence

Colorectal cancer can be prevented: there are a variety of histological types of colonic polyps, such as juvenile, inflammatory, hyperplastic, and adenomatous. For the majority of colorectal cancer (CRC) patients, the adenocarcinoma arises from an adenomatous polyp. Polyps of 2 cm or larger have about 50% incidence of cancer, compared to a 1% risk in adenomas less than 1 cm in size.

Adenomatous polyps are a premalignant condition, and their identification and removal before becoming malignant prevents the development of CRC. These polyps can arise anywhere in the colon, but (as is the case for CRC) they are more frequently seen in the left colon. The majority of polyps are completely asymptomatic, but the occurrence of occult bleeding does increase as they grow. Unfortunately, polyps can still be missed, even with occult blood testing of the stool, since the blood loss may be intermittent. Examples of different polyps are seen in Figure 4. Three histologic types of adenomatous polyps occur: tubular, tubulovillous and villous. The malignant potential is greatest in villous polyps (40%) and lowest in tubular polyps (5%), with an intermediate risk in tubulovillous polyps (22%). The malignant potential may also be described pathologically .
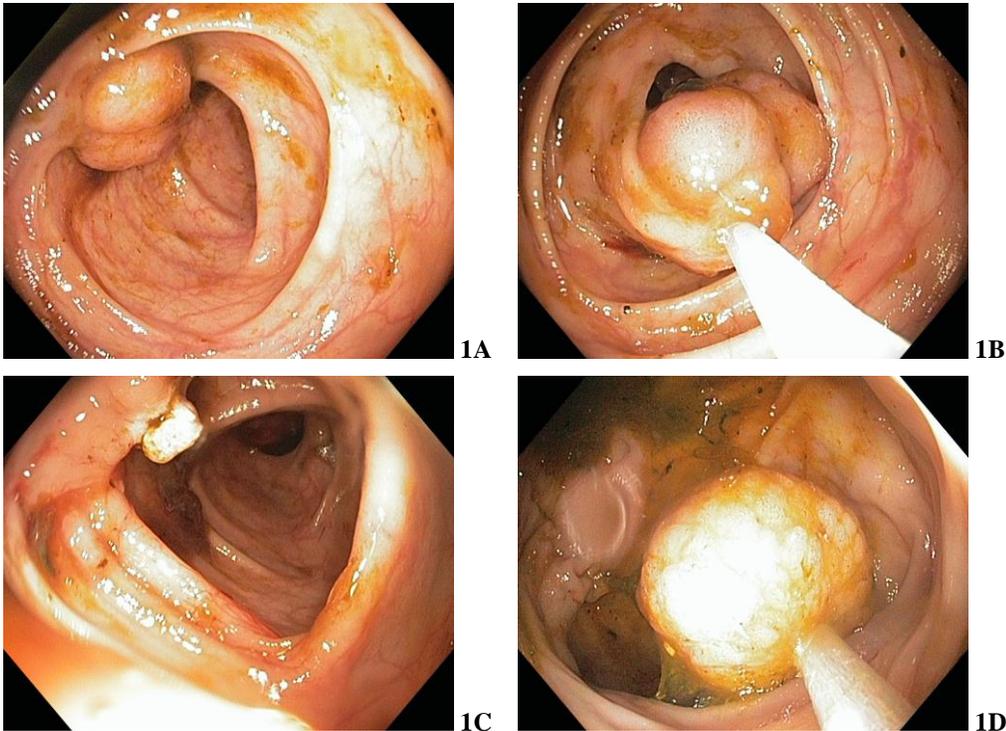
Figure 1. Demonstration of adenomatouspPolyp removal at colonoscopy.

Figure 1A. Sigmoid colon polyp.

Figure 1B. Polyp snared and ready to transect the stalk of the polyp using electrical current passing through the metal snare wire to completely remove the polyp. The normal tissue of the stalk is seen to the right of the snare in the middle of the image.

Figure 1C. The base of the resected polyp with the cautery burn evident on the remainder of the stalk.

Figure 1D. The polyp has been grasped in a Roth net, passed down the operating channel of the colonoscope after the snare is removed and polyp is now removed from the colon to be sent for pathology diagnosis. because the degree of "dysplasia": can indicate a greater the risk of malignancy with higher grade dysplasia (ie. High grade versus low grade dysplasia). These polyps can often be completely removed by snare polypectomy at colonoscopy if they are pedunculated on a stalk, but sessile polyps that carpet a wide area of colonic mucosa (often villous polyps) can usually be completely removed only by colonic resection surgery.
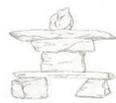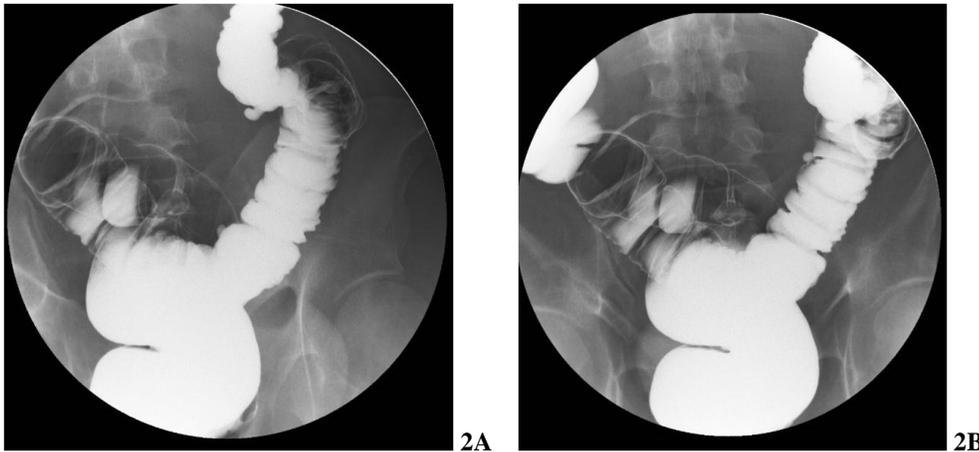
Figure 2A. & 2B. Filling defect in the mid sigmoid on barium enema, consistent with a 16 mm pedunculated polyp. The white arrow identifies the polyp." Again, I have included the original image as well as the image on a Powerpoint slide to indicate where the arrow should go.

Since polyps precede cancer and removal of polyps "cures" the CRC, screening colonoscopy reduces the incidence of cancer. Other polyps as well may be present at the initial or index screening colonoscopy, and polyps and cancer tend to recur. This sets the stage for the rationale for performing follow-up surveillance colonoscopies (colon cancer surveillance program). The best time interval for this surveillance when polyps have been found in the past is probably every five years; longer intervals between surveillance colonoscopies may be safe but have yet to be tested. The cost-effectiveness of screening all persons over the age of 50 has not been proven but screening has been shown to reduce the incidence of CRC, especially in high risk groups for developing colon cancer.

LEARNING POINTS

- o Because of the colonic polyp CRC sequence, CRC may be prevented by the early detection of adenomatous polyps, followed by a surveillance program
- o Colonoscopy is the "gold standard" for screening for colonic polyps
- o All persons over the age of 50 should have a colonoscopy
- o Persons with a family history of colonic adenomas or CRC should have a colonoscopy, often before the age of 50

Screening for CRC has become very controversial as to the correct intervals, who to screen and the best tools to use for screening. The Canadian Association of Gastroenterology has published guidelines for CRC screening; there are guidelines published by the American Gastroenterological Association and the British Society of Gastroenterology.

3. Colon Cancer Screening

Particular conditions have been associated with an increased risk of CRC. All patients with the following conditions require some form of regular colon surveillance to detect polyps/cancer at its earliest stage to improve survival. The autosomal dominant "polyposis" syndromes of Familial Adenomatous Polyposis (FAP), Gardner 's syndrome and Turcot's syndrome are now recognized to all be various expressions of disease caused by mutations of the APC gene (autosomal dominant inheritance). These conditions are manifested by early onset (usually before age 30) of innumerable colonic adenomatous polyps that eventually and invariably lead to CRC usually before age 40. Since the colon has too many polyps to remove by endoscopy-guided polypectomy these patients are referred at an early age for total proctocolectomy to remove the risk of CRC.

Most patients opt for an ileal pouch with anastomosis to the anal sphincters (ileal pouch, anal anastamosis IPAP), rather than an ileostomy (Brooke's procedure), with the effluent. After colectomy these patients still need regular upper GI endoscopic surveillance, to detect, biopsy, and remove adenomatous polyps from the stomach and duodenum. They also need the ileal pouch endoscopically examined to ensure there are no changes from the transitional mucosa left behind at the anastomosis of the ileal pouch to the anus.

Genetic screening should be undertaken on persons with FAP, and their family members, looking for mutations in the FAP gene, which is the cause of this autosomal dominant disease.

There are other families (site-specific colorectal cancer, family cancer syndrome) that have a high risk of colon cancer (autosomal dominant inheritance), with more than two first-degree relatives in at least two generations, having had colon cancer or adenomatous polyps and at least one of the relatives has to be under age 50. This disease is called hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. All patients should be entered into a colon cancer surveillance program of colonoscopy and/or air contrast barium enema starting at age 21. Patients with HNPCC are to have the colon screened every two years until age 40, when they should have yearly screening. Ideally, screening is done with colonoscopy if possible as polyps are frequently encountered and need to be removed when found. Female patients with HNPCC also have an increased risk of endometrial and ovarian cancer and need yearly pelvic ultrasound and/or vaginal ultrasound after age 40 to identify suspicious lesions as early as possible.

The other group of patients at increased risk of cancer who should all be screened are those patients who have had a colon cancer resected. Colonoscopy should be done either preoperatively or within a year of surgery. It should be repeated three years post surgery, and then every five years if there are no polyps or evidence of recurrent tumor. If there is any concern about complete resection of the original tumor, earlier surveillance would be recommended (less than one year after surgery).

Also at a high risk for CRC are patients with chronic ulcerative colitis (UC) for more than 8 to 10 years; this risk also appears to be present in patients with Crohn's pancolitis. The patients at highest risk are those who have had total colon involvement, as well as and those with disease up to and including the hepatic flexure (subtotal colitis). Patients with proctosigmoiditis are at least risk – probably not greater than the general population. Curiously, the risk of CRC does not correlate with the degree of disease activity. Therefore, patients with just one bout of proven subtotal ulcerative colitis would have an increased risk of CRC after 8 to 10 years of disease, and the younger the patient at the time of onset of his or her disease, the greater the cumulative risk of cancer will be for that patient. Unlike those who experience the "polyp–carcinoma sequence,"

patients with UC do not develop adenomatous polyps before they develop cancer. Therefore, after the first 8-10 years of UC, they require colonoscopy about every one to two years, with multiple endoscopic biopsies of the colon performed to identify dysplasia of the mucosa. Particular attention should be paid to "elevated" or "flat" lesions seen at colonoscopy, where the incidence of early colon cancer is high. If there is dysplasia, either "high grade" or "low grade," colectomy should be recommended to the patient.

Screening for CRC is also recommended for all "average risk" persons age 50 years or above. If a person has a first degree family member with CRC younger than age 60 years, then the person is at increased risk of colorectal cancer and imaging of the colon with colonoscopy or CT colonography should be considered. Otherwise, all individuals over age 50 should have at least stool testing for occult blood and/or flexible sigmoidoscopy.

IMAGING OF RECTAL CANCER

Current management strategies for rectal cancer include preoperative radiation and chemotherapy for patients at increased risk of local recurrence. Accurate preoperative staging helps to stratify the patient's risk. Superficial rectal cancers can be imaged with endorectal ultrasound. Larger tumours require a high spatial resolution MRI with a dedicated phased array coil. This allows evaluation of the rectal wall, the mesorectal fascia, local invasion of pelvic structures and the presence of regional adenopathy. These techniques can identify the patients who will benefit from preoperative chemotheraphy or radiotherapy. Figure 3A is an axial T2 weighted MRI image demonstrating a circumferential enhancing mass from the 5 o'clock to 1 o'clock position in the rectum (long white arrows). There is transmural extension and local adenopathy in the mesorectal fat (short black arrows). Figure 3B is a sagittal T2 weighted MRI image which shows the craniocaudal extent of the mid to high rectal tumour (white arrows).

Figure 3A
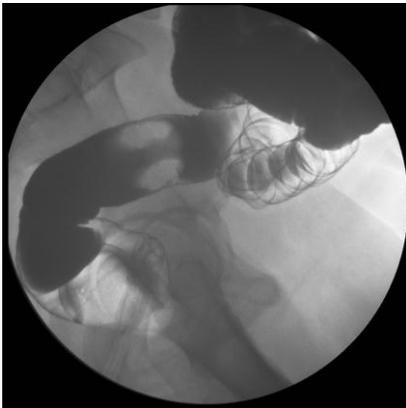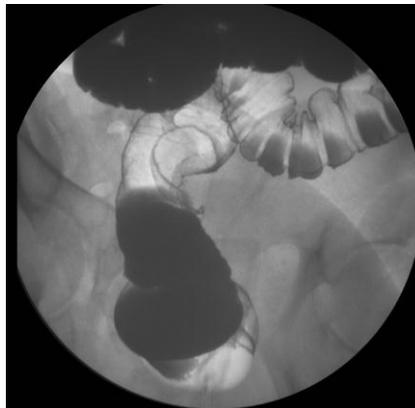
Figure 3B

Figure 4. A 5 cm broad based filling defect in the upper rectum on double contrast barium enema.
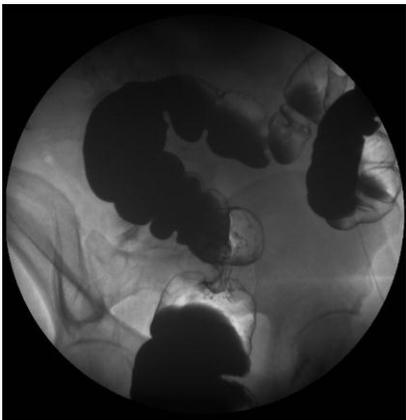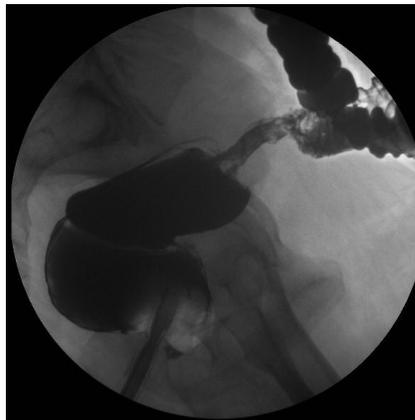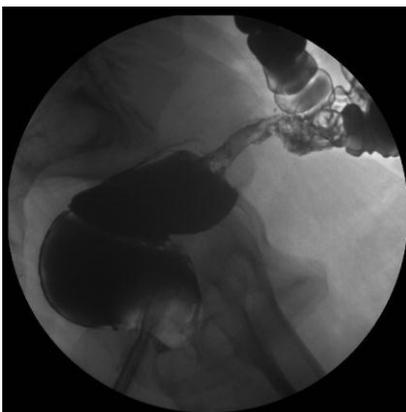
Figure 5. Barium enema xray images of an annular lesion in the rectosigmoid colon compatible with primary carcinoma

4. Colonic Obstruction

Acute colonic obstruction is a surgical emergency that must be recognized early and dealt with expeditiously in order to avoid the high fatality rate due to colonic perforation. The highest risk patients for associated colonic perforation are those with an intact ileocecal valve (this does not allow air to reflux back into the small bowel from the obstructed colon). The cecum is the most frequent colonic site of perforation, because wall tension is highest in the bowel with the largest diameter (Laplace 's law).

Patients with more chronic colonic obstruction usually have pain as a prominent symptom, with constipation often preceding the complete obstruction. Patients may initially present with diarrhea as the bowel distal to the obstruction empties. Alternatively, the diarrhea may be persistent, especially with a partial obstruction, because of the increased intestinal secretion proximal to the obstruction, or to "overflow" diarrhea, the passage of proximally secreted fluid which leaks around an obstruction from, for example, stool or tumour.

The small intestine is the most common site of intestinal obstruction because of its narrower caliber of the bowel. Similarly the left colon is the most common site for colonic obstruction, especially since the stool is more formed in the left colon and unable to pass through a narrowed lumen.

On physical examination the general state of the patient depends upon the duration of the obstruction. With a recent sudden obstruction the patient will be in extreme pain, will often have distention of the abdomen (if the ileocecal valve is intact) and they may initially describe diarrheal stool as the bowel distal to the obstruction is emptied. Abdominal palpation may demonstrate a mass lesion at the site of the obstruction. Prompt identification of the site of obstruction is mandatory, with the use of supine and erect abdominal x-rays.

An urgent surgical consultation is required if there is a complete colonic obstruction: the rectum will be empty of air with dilation of more proximal colon. Many patients present with a more gradual history. If they have had protracted diarrhea up to the point of obstruction, the amount of abdominal pain may be less. They may have abdominal distention, but be less tender on abdominal exam. They will often show signs of dehydration. Fever and an abdominal mass is particularly common in patients with diverticulitis and a resulting colonic obstruction.

A third type of colonic obstruction can be seen that is actually a form of ileus limited to the colon, and is sometimes referred to as Ogilvie's syndrome. These patients are most often seen in intensive care units, but the condition can also occur postoperatively (even when no bowel surgery has been performed). As with a "mechanical" bowel obstruction (described above), patients with Ogilvie's syndrome may have marked abdominal distention. Frequently they have little abdominal pain, and the abdominal x-rays show a picture of dilated colon with impaired movement of air into the distal colon.

Once a diagnosis of colonic obstruction has been made, the site of obstruction should be determined by plain abdominal x-rays and/or with a water soluble contrast enema (such as iothalamate meglumine) to identify whether urgent surgery is indicated.

If investigations do not confirm obstruction of the colon, colonic ileus can often be treated safely by neostigmine 2.0 to 2.5 mg IV. Bradycardia may occur with this medication, and all patients must receive cardiac monitoring.

The majority of patients respond well to neostigmine and this avoids the need for urgent colonoscopy and the increased risk of perforation of the colon due to poor visualization in the unprepared colon. However, if the endoscopist is able to decompress the lumen by suctioning the

excess air, a decompression tube can sometimes be placed high in the colon to facilitate removing colonic air following the procedure.

There are many causes of colonic obstruction (Table 4). Colon cancer and diverticulitis are the most common causes. Most colon cancers that obstruct are in the left colon. They cause circumferential disease or "apple-core" lesions (so called because of the irregular mucosal appearance with luminal narrowing seen at x-ray). Diverticulitis commonly occurs in the sigmoid colon, where diverticular disease is most common. The acute abscess formation with swelling of the inflamed diverticulum compresses and obstructs the affected sigmoid colon. The person with colonic obstruction due to Ogilvie's syndrome may initially have been considered to be due to a cancer or diverticulitis, but abdominal film and contrast x-ray demonstrates a patent lumen.

Less common causes of colonic obstruction are hernias, in which a loop of colon (usually sigmoid) becomes strangulated and the bowel is acutely obstructed. This is a much more common cause of small bowel obstruction. Strictures in the colon can also be associated with obstruction, especially when they occur in the left colon. These can occur with Crohn's colitis, after a bout of ischemic colitis or at the site of anastomosis following colonic surgery. If possible, this later cause of obstruction should always be visualized endoscopically, since most colonic resections are for cancer and the possibility of a local cancer recurrence can complicate a postsurgical stricture.

Intussusception can occur in the colon, and in adults it almost always occurs at the site of a polyp, which "leads" the intussusception. Typically, this will cause intermittent acute bowel obstruction associated with severe pain and often rectal bleeding from the vascular compromise produced in the intussuscepting bowel. Because of the intermittent nature of the obstruction, a diagnosis may not be made until after repeated attacks. A barium enema should always be considered in this setting, as it identifies the mucosal lesion "leading" the intussusception and can occasionally be used to reduce the intussusception without the need for urgent surgery. Volvulus of the colon tends to happen in the cecum and/or the sigmoid colon, because the mesentery is long and redundant in these areas and cause the bowel to rotate upon itself. This can be a surgical emergency, since the affected bowel will strangulate if the volvulus is not relieved quickly.

Table 3. Causes of colonic obstruction

➢ Common	➢ Others
o Left-sided cancer	o Hernia
o Diverticulitis	o Strictures
o Ogilvie's syndrome	o Crohn's
	o Postischemic
	o Postsurgical
	o Intussusception
	o Volvulus
	o Adhesions

Again, an urgent barium enema may be able to reduce the volvulus, thus allowing a more elective surgical procedure to correct the problem. A sigmoid volvulus will usually be reduced by this approach, and success with colonoscopic decompression of a sigmoid volvulus has been reported. A cecal volvulus may not be easily treatable with either a barium enema or

colonoscopic therapy. Thus, surgical advice should be sought urgently if cecal volvulus is diagnosed.

Adhesions are often described as a common cause of bowel obstruction, but this is probably true only for small bowel obstruction. Since much of the colon is retroperitoneal or on a short mesentery, adhesive disease with obstruction of the colon is rare. However, it can occur, particularly in the sigmoid colon if the mesentery is quite long, particularly after pelvic operations.

4.1. Megarectum

When the rectum is enlarged, further investigations are required to exclude other causes, particularly Hirschsprung's disease. The majority of patients with constipation and a dilated rectum and/or colon at proctosigmoidoscopy or barium enema have idiopathic or acquired megarectum.

A useful guideline for the diagnosis of a "megarectum" is a rectal diameter of greater than 6 cm on a lateral film at the level of the S2 vertebral body. These patients can often present in childhood (many of them presenting with encopresis) and in the elderly with a fecal impaction. The cause of the megarectum is unknown, but if the onset is in childhood it may be the result of chronic stool holding by the child, leading to progressive distention of the rectum and eventual loss of awareness of rectal distention. Once this has occurred the child can no longer recognize when stool is present in the rectum. The distention of the rectum causes chronic inhibition of the resting tone of the internal anal sphincter. This leads to the loss of control of liquid or semisolid stool that passes by the fecal impaction without the patient being aware of it.

4.2. Hirschsprung's Disease

The majority of persons with this disorder present soon after birth or in early childhood. wherein Hirschsprung's disease, variable lengths of distal colon have no myenteric plexus neurons. The distal colon remains contracted due to this loss of neurons, and the inability to dilate, whereas the normal proximal colon dilates as it fills with stool. Most of these patients present early in life with constipation and colonic obstruction, and require surgery.

However, a few patients have a very short segment of denervated distal colon, so that they can overcome the obstruction by forcing stool out of the rectum. They usually have lifelong constipation; the normal rectum proximal to the denervated segment dilates over time so that the patient presents with constipation and a "megarectum." These patients rarely have the fecal incontinence or fecal "soiling" as seen with idiopathic megarectum, since the internal anal sphincter and denervated distal rectum maintain a high resting tone.

Anorectal manometry, will demonstrate an abnormal rectoanal inhibitory reflex (Figure 9). However, a definite diagnosis requires deep rectal biopsy from the denervated segment, which will show absence of the myenteric plexus ganglion cells and hypertrophy of nerve fiber bundles.

It should be added that an identical condition can be acquired with Chagas' disease from South America , which attacks the myenteric plexus and other autonomic ganglion cells. Persons with Chagas' disease can also present with achalasia, intestinal pseudo-obstruction, as well as cardiac arrhythmias. These patients will also have an absent rectoanal inhibitory reflex if the disease involves the rectal myenteric plexus.
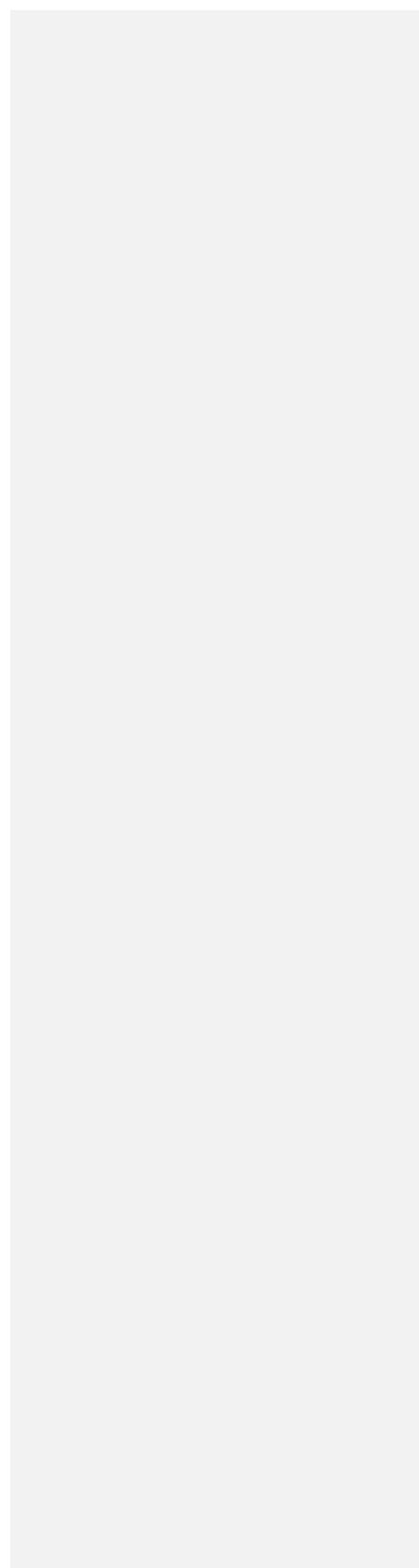
Chapter 14: Evaluation of Defecation and Anorectal Complaints
M. Burnstein, G.K. Turnbull

This section will review the symptoms associated with anorectal pathology, and the techniques of anorectal examination.

1. History

As in most of medicine, taking a careful history is the most productive step in leading to a diagnosis. In the evaluation of the patient with anorectal complaints, there are a limited number of questions to be asked.

1.1. Pain

There are three common lesions that cause anorectal pain: fissure in ano, anal abscess, and thrombosed external hemorrhoid. If the pain is sharp, and occurs during and for a short time following bowel movements, a fissure is likely. Continuous pain associated with a perianal swelling usually stems from thrombosis of perianal vessels, especially when there is an antecedent history of straining, either at stool or with physical exertion. An anal abscess will also produce a continuous, often throbbing pain, which may be aggravated by the patient's coughing or sneezing. Anorectal abscesses are generally associated with local signs of inflammation. The absence of an inflammatory mass in the setting of severe local pain and tenderness is typical of an intersphincteric abscess. The degree of tenderness usually prevents adequate examination, and evaluation under anesthesia is necessary to confirm the diagnosis and to drain the pus.

Anal pain of any etiology may be aggravated by bowel movements. Tenesmus, an uncomfortable desire to defecate, is frequently associated with inflammatory conditions of the anorectum. Although anal neoplasms rarely produce pain, invasion of the sphincter mechanism may also result in tenesmus. Tenesmus with urgency of evacuation suggests proctitis.

Transient, deep-seated pain that is unrelated to defecation may be due to spasm of the levator ani muscle ("proctalgia fugax"). Anorectal pain is so frequently, and erroneously, attributed to hemorrhoids, that this point bears special mention: pain is *not* a symptom of uncomplicated hemorrhoids. If a perianal vein of the inferior rectal plexus undergoes thrombosis, or ruptures, an acutely painful and tender subcutaneous lump will appear. This is the "thrombosed external hemorrhoid." Internal hemorrhoids may prolapse and become strangulated to produce an acute problem of anorectal pain, tenderness, and mucous, bloody discharge. Gangrene and secondary infection may ensue.

1.2. Bleeding

The nature of the rectal bleeding will help determine the underlying cause. However, the clinician must remember that the historical features of the bleeding cannot be relied upon to define the problem with certainty. Bright red blood on the toilet paper or on the outside of the stool, or dripping into the bowl, suggests a local anal source, such as a fissure or internal hemorrhoids. Blood that is mixed in with the stool, or that is dark and clotted, suggests sources proximal to the anus. Melena is always due to bleeding from more proximal pathology in the colon, small intestine, duodenum, or stomach. A history of bleeding associated with painful defecation, suggests a fissure. The same bleeding pattern without pain suggests internal hemorrhoids; this may be associated with some degree of hemorrhoidal prolapse. Bleeding and diarrhea may occur with inflammatory bowel disease.

When bleeding is associated with a painful lump and is not exclusively related to defecation, a thrombosed external hemorrhoid is likely. Bleeding associated with a mucopurulent discharge and tenesmus may be seen with proctitis, or possibly with a rectal neoplasm.

Bleeding per rectum is an important symptom of colorectal cancer, and although this is not the most common cause of hematochezia, it is the most serious and must always be considered. This does not mean that every patient who passes blood must have total colonoscopy. If the bleeding has an obvious anal source, it may be prudent not to proceed with a total colon examination, especially in a patient at low risk for colorectal neoplasms (i.e., age under 50 years; no history of Crohn's or ulcerative colitis; no family history of colon cancer; and no personal history of colorectal neoplasms). However, if bleeding persists after treatment of the anal pathology, more ominous lesions must be excluded.

1.3. Prolapse

In evaluating protrusion from the anal opening, there are several relevant questions: Is the prolapse spontaneous or exclusively with defecation? Spontaneous prolapse is usually from hypertrophied anal papillae or complete rectal prolapse, rather than from internal hemorrhoids. Does the prolapsing tissue reduce spontaneously (as with second-degree internal hemorrhoids), or does it require manual reduction (as with third-degree internal hemorrhoids or with many cases of complete rectal prolapse)? The patient may be able to describe the size of the prolapsing tissue, and this may suggest the diagnosis. Complete rectal prolapse (procidentia) must be distinguished from mucosal prolapse or prolapsing internal hemorrhoids. Procidentia occurs mainly in women (female:male = 6:1), with a peak incidence in the seventh decade. Procidentia is often associated with fecal incontinence. In later stages, protrusion occurs even with slight exertion from coughing or sneezing. The extruded rectum becomes excoriated, leading to tenesmus, mucus discharge and bleeding.

Examination of the patient with procidentia usually reveals poor anal tone, and with the tissue in a prolapsed state, the mucosal folds are seen to be concentric, whereas with prolapsed hemorrhoids there are radial folds. Rarely, a large polypoid tumor of the rectum may prolapse through the anal canal.

1.4. Perianal mass

A painful perianal lump may be an abscess, or a thrombosed external hemorrhoid.

Knowing whether there has been a discharge of blood or pus may be helpful. An intermittent mass suggests a prolapsing lesion. External or "skin" tags are very common deformities of the anal margin. They may be the result of previous or active fissure disease, or the sequelae of a thrombosed external hemorrhoid. Condylomata acuminata – or venereal warts – are caused by a sexually transmitted virus. The perianal skin is frequently affected, and the condition occurs with greatest frequency in men who have sex with men.

The differential diagnosis of a perianal mass also includes benign and malignant neoplasms.

1.5. Pruritus ani

Itching is commonly associated feature of many anorectal conditions, especially during the healing phase or if there is an associated discharge. Pruritus ani may also be an isolated symptom, or the patient's primary complaint. As a chief complaint, pruritus may be caused by

infections (e.g., pinworms, condylomata, Candida) or skin conditions (e.g., contact dermatitis, psoriasis).

More commonly, no specific underlying pathology is identified, and the problem is idiopathic, and is treated symptomatically.

Idiopathic pruritus ani is more common in men, and is typically worse at night. When chronic, the characteristic changes of hypertrophy and lichenification, nodularity, scarring and fissuring of the skin become apparent.

1.6. Discharge

Although mucus is a normal product of the colorectal mucosa, it is not normally seen in the stool. Increased mucus may be the result of proctocolitis or a colorectal neoplasm, especially a villous adenoma of the rectum. Both inflammatory and neoplastic conditions may present with mucus and blood. Phosphate enemas are irritating, and often produce copious production of mucus. Patients with the irritable bowel syndrome may complain of mucous containing stools. Mucus staining of the underclothes may be associated with prolapsing rectal tissue.

When the staining has a fecal component, or when there is associated inability to control gas (the passing of flatus), or to discriminate gas from solids within the rectum, a disturbance of the continence mechanism exists. The frequency of "accidents" (from incontinence), or the need to wear pads during the day or night, will help indicate the magnitude of the problem. The discharge may arise from an obvious external lesion – e.g., blood from a thrombosed external hemorrhoid, or pus from an abscess, from the external opening of a fistula, from a pilonidal process or from perianal hidradenitis suppurativa.

Other issues that will prove helpful in coming to a diagnosis of anorectal pathology include bowel habits, associated medical conditions, medications, sexual practices, travel history and family history.

2. Examination

The patient about to undergo examination of the anorectum may not only be embarrassed, but also afraid of impending pain and discomfort. Explanation of the examinations to be performed, and reassurance, will lessen the patient's anxiety and contribute greatly to patient cooperation.

Some physicians prefer that the patient will have been given an enema to clear stool from the rectum.

The four steps in anorectal evaluation are inspection, palpation, anoscopy and proctosigmoidoscopy.

2.1. Positioning

The patient is placed either in the left lateral position, or preferably in the prone-jackknife position. The prone-jackknife position requires a special table that tilts the head down and raises the anorectal region, with the buttocks tending to fall apart. This provides the best and easiest access to the area for the examiner, although patient comfort may be less. The left lateral (Sims') position has the advantages of patient comfort and of being suitable for any examining table, bed or stretcher. The patient's buttocks are allowed to protrude over the edge of the table, with hips flexed and knees slightly extended. The examiner may sit or stand. The patient is unable to see "what's going on back there," and it is important to continually explain what you are doing and what can be expected.

2.2. Inspection

Looking at the anal area may reveal external pathology. The resting anal aperture should be observed: a patulous opening may be seen with procidentia, sphincter injury or neurologic abnormality. Straining and squeezing by the patient may provide information about anorectal function. Gentle spreading of the buttocks may elicit pain in a patient who has an anal fissure. Asking the patient to strain down may show protruding: internal hemorrhoids or procidentia. However, if procidentia is suspected, it should be sought with the patient squatting or sitting at the toilet.

2.3. Palpation

A disposable plastic glove and water-soluble lubricant are required. The patient is told that a finger will be gently placed into the rectum. While one hand separates the buttocks, the index finger is placed on the anal verge, and with the patient bearing down, (thereby relaxing the anus), the digit is advanced into the anal canal. The patient should be cautioned that they may feel as if they need to have a bowel movement.

A methodical approach is best. Palpation anteriorly checks the prostate in males, and the cervix in females. The finger then sweeps backward and forward to palpate the rest of the circumference of the anorectum. This may be the only part of the examination that identifies submucosal lesions, which may easily go undetected by endoscopy. Resting tone, the patient's ability to squeeze, the location of tenderness, or a palpable abnormality should be precisely recorded.

2.4. Anoscopy

The anoscope is the optimal instrument for examining lesions of the anal canal. It is not a substitute for proctosigmoidoscopy, and the proctosigmoidoscope does not provide as satisfactory a view of the anal canal as does the anoscope. The best type of anoscope instrument is end-viewing, with an attached fiberoptic light source.

2.5. Proctosigmoidoscopy

The rigid 25 cm sigmoidoscope (or proctoscope) is arguably the best instrument for examining the rectum. A barium enema, because of the balloon-tipped catheter used in administering the contrast material, does not adequately evaluate the rectal ampulla, and is never a sufficient workup of a lower GI complaint. A variety of rigid sigmoidoscopes are available: disposable or reusable, in a range of diameters (1.1 cm, 1.9 cm, 2.7 cm), and with proximal or distal lighting. The 1.9 cm instrument provides good visibility with minimal patient discomfort. The instrument includes a 25 cm tube, a magnifying lens, a light source, and a bulb attachment for air insufflation. Long swabs may be helpful in maintaining visibility, but suction is best. The long swabs are also useful to determine if there is mucosal friability.

A single Fleet® enema provides excellent preparation of the distal bowel and should be used just before the examination. The Fleet® enema may produce transient mucosal changes, and if inflammatory bowel disease is suspected, it should be avoided.

The digital examination has set the stage for instrumentation by permitting the sphincter to relax. With the tip well lubricated, the sigmoidoscope is inserted and passed up into the rectum. As always, the patient is informed of what is being done, and is reassured that the

sensation of impending evacuation is caused by the instrument, and that the bowels are not about to move.

Air insufflation should be kept to a minimum, as it may cause discomfort, but it is of value both on entry and on withdrawal in terms of demonstrating the mucosa and lumen and in assessing rectal compliance and the presence of normal sensation of rectal distention. Advancement should occur only with the lumen, clearly in sight. When the lumen is "lost," withdraw and redirect the sigmoidoscope in order to regain visualization of the lumen. As the rectosigmoid is reached (approximately 15 cm from the anus), the patient should be warned of possible cramping discomfort that will disappear as the scope is removed. Sometimes, even with experience, the rectosigmoid angle cannot be negotiated, and the examination should be terminated. Most importantly, the patient should not be hurt or caused significant discomfort. The scope should be withdrawn making large circular motions, carefully inspecting the circumference of the bowel wall, flattening the mucosal folds and valves of Houston. The posterior rectal wall in the sacral hollow must be specifically sought out, or it will be missed.

In most large studies, the average depth of insertion of the rigid sigmoidoscope is 18–20 cm; the full length of the instrument is inserted in less than half the patients.

Perforation of the normal rectum by the sigmoidoscope is extremely rare (1 in 50,000 or less). However, advancing the instrument or insufflating air may be hazardous in settings such as inflammatory bowel disease, radiation proctitis, diverticulitis and cancer. Of course, biopsy and electrocoagulation have to be performed with care and with knowledge of the technique and equipment. The significance of bacteremia following anorectal manipulations is controversial, and has been reported in 0–25% of proctoscopies.

3. Specific Anorectal Problems

This section will briefly review some of the more common anorectal problems.

3.1. Hemorrhoids

3.1.1. Background

The upper anal canal has three sites of thickened submucosa containing arterioles, venules and arteriovenous communications. These three vascular "cushions" are in the left lateral, right anterior and right posterior positions. Minor cushions may lie between the three main ones. The cushions are held in the upper anal canal by muscular fibers from the conjoined longitudinal muscle of the intersphincteric plane. Hemorrhoids exist when the anal cushions prolapse after disruption of their suspensory mechanism, or when there is dilation of the veins and arteriovenous anastomoses within the cushions. There are various theories for the development of internal hemorrhoidal disease: raised intra-abdominal pressure, pressure on the hemorrhoidal veins by an enlarging uterus, poor venous drainage secondary to an overactive IAS, or straining at stool with a resultant downward displacement of the cushions.

Skin tags are projections of skin at the anal verge. They may be the result of previous thrombosed external hemorrhoids, fissure-in-ano, or inflammatory bowel disease. *External hemorrhoids* are dilated veins of the inferior hemorrhoidal (rectal) plexus. This plexus lies just below the dentate line, and is covered by squamous epithelium. *Internal hemorrhoids* are the symptomatic, enlarged submucosal vascular cushions of the anal canal. The cushions are located above the dentate line, and are covered by columnar and transitional epithelium. First-degree hemorrhoids produce painless bleeding but do not protrude from the anal canal. Anoscopy, first-degree hemorrhoids are seen to bulge into the lumen. Second-degree hemorrhoids protrude with

bowel movements, but reduce themselves spontaneously. Third-degree hemorrhoids prolapse outside the anal canal, either spontaneously or with bowel movements, but require digital reduction. Fourth-degree hemorrhoids are always prolapsed, and cannot be reduced.

3.1.2. Diagnosis and treatment
3.1.2.1. Thrombosed external hemorrhoids

As a rule, external hemorrhoids are asymptomatic until there is the complication of thrombosis (intravascular clot) or rupture (perianal hematoma). In either case, the presentation is severe pain with a perianal lump, often after straining.

The natural history is one of continued pain for 4 to 5 days, then slow resolution over 10 to 14 days. The treatment depends on the severity of the pain and the timing of presentation. A patient who presents within 24 to 48 hours with severe pain is best dealt with operatively. Under local anesthesia, the involved perianal vessel and clot are excised. The wound may be left open or may be closed. Simple evacuation of the thrombus is less effective.

A patient presenting later, after 3 to 4 days, is generally advised to take frequent warm baths, a bulk laxative, a surface-active wetting agent, and oral analgesics. This regimen is also prescribed post-excision.

3.1.2.2. Internal hemorrhoids

Painless, bright red rectal bleeding (usually with or following bowel movements) is the most common symptom of internal hemorrhoids. Blood appears on the toilet paper or on the outside of the stool, or drips into the bowl. It is very rare for the volume of blood lost from internal hemorrhoids to be sufficient to explain iron deficiency anemia and further workup is always indicated to ensure that a colon cancer or bowel inflammation is not missed.

Prolapse with defecation or other straining activities is also a common symptom of internal hemorrhoids. Chronic prolapse is associated with mucus discharge, fecal staining of the underclothes and pruritus. Anal sphincter spasm may result in thrombosis and strangulation of prolapsed hemorrhoids. This presents as an acute painful, discharging, edematous mass of hemorrhoids. Inspection will identify the later stages of the disease, especially when the patient is asked to bear down. Digital examination can rule out other pathology, as well as assess the strength of the sphincters. A palpable abnormality suggests some other process.

Anoscopy provides a diagnosis in first- and second-degree disease. With the anoscope in place, the patient is once again asked to strain, and the degree of prolapse observed. Proctosigmoidoscopy should always be performed to exclude other diseases, particularly rectal neoplasms and inflammatory bowel disease.

If the symptoms are at all atypical, or the physical findings leave any doubt about the source of blood, a colonoscopy should be performed to examine the entire bowel. In patients over the age of 50, it is reasonable to take the opportunity to screen (or to practice "case-finding") for colorectal cancer by performing colonoscopy. Occasional bleeding, especially if it is related to the passage of hard stools or straining, should be managed by improving bowel habits using a high-fiber diet and bulk agents (e.g., psyllium). If bleeding persists or is frequent, intervention is indicated, and in most cases should take the form of rubber-band ligation. Prolapsing hemorrhoids that reduce spontaneously, or that can be easily reduced, are also nicely treated by rubber-band ligation. If prolapsing tissue is not easily reduced, or if there is a significant external component, surgical hemorrhoidectomy offers the best cure. Similarly, prolapsed, thrombosed internal hemorrhoids should be surgically excised. The specific operative

options for internal hemorrhoidal disease, and the description of these procedures, are beyond the scope of this text.

3.1.2.3. Rubber-band ligation

In this technique, strangulating rubber bands are placed tightly at the cephalad aspect of the internal hemorrhoids. The banded tissue infarcts and sloughs over the next week, resulting in reduction of hemorrhoidal tissue, as well as fixation of the residual hemorrhoid in the upper anal canal. The absence of somatic pain fibers above the dentate line renders this a relatively painless procedure, as long as the rubber bands are properly positioned. This cuts off the blood supply. Banding is a simple office procedure requiring an anoscope and a ligator. In general, only one or two areas are banded at a time, so that several treatments are often required. Long-term success is expected in approximately 75% of patients with second degree hemorrhoids. Pain, bleeding and infection are rare complications.

3.1.2.4. Hemorrhoidectomy

Since the popularization of rubber-band ligation, excisional hemorrhoidectomy is much less frequently performed. The important principles of all excisional procedures are the removal of all external and internal hemorrhoids, protection of the internal anal sphincter from injury, and maintenance of the anoderm, so as to avoid anal stenosis.

3.2. Fissure In Ano

A fissure *in ano* (often simply called a "fissure") is a linear crack in the lining of the anal canal, extending from the dentate line to the anal verge. It is seen equally in men and women, and at all ages, but is a common entity in young adults. It is encountered mainly in the posterior midline (6 o'clock position). If a fissure persists, secondary changes occur. These include the "sentinel pile" at the distal end of the fissure, the "hypertrophied anal papilla" at the proximal end, exposure of internal anal sphincter fibres at the base of the fissure, fibrotic fissure edges and widening of the fissure.

3.2.1. Pathogenesis

Fissure *in ano* is probably the result of straining to have a bowel movement, or trauma during the passage of hard stool. Not all patients with fissure in ano give a history of "constipation." While most fissures will readily heal with an appropriate change in bowel habits, and stool composition, some fissures persist. This may be due to continued trauma or to spasm (actually, sustained hypertonicity) of the IAS.

There is an association between fissures and Crohn disease, and this association should be kept in mind.

3.2.2. Diagnosis

Pain with defecation is the chief complaint of a fissure. The pain may persist for minutes to hours. Bright red blood is often seen on the toilet paper and on the surface of the stool. The patient with an edematous, tender skin tag (sentinel pile) may complain of a painful hemorrhoid. The patient may become constipated in response to painful defecation from a fissure.

With gentle separation of the buttocks, most fissures will be visible. The sentinel pile of a chronic fissure may be the initial finding. With acute fissures, digital and anoscopic examination are usually not possible because of local tenderness. However, these examinations should be

performed later to rule out other pathology. With chronic fissures, anoscopy reveals the defect in the anoderm, with exposed muscle fibers of the IAS at the fissure base. The hypertrophied anal papilla may be seen. Fissures off the midline should raise the possibility of other diseases. Crohn disease may be associated with atypical-looking fissures that are off the midline and have atypical symptoms. Anal and rectal carcinoma should be palpably different from fissures. If any doubt exists about the diagnosis, a biopsy should be performed. A syphilitic chancre may occasionally look like an idiopathic fissure.

3.2.3. Treatment

The mainstay of therapy for acute fissures is to achieve daily soft bowel movements. This will prevent further tearing, allowing most acute fissures to heal within one to two weeks. A high-fiber diet supplemented with bulk agents and surface-active wetting agents will accomplish the desired effect.

Warm tub baths are soothing and cleansing, and transiently reduce spasm. The reduction of internal anal sphincter hypertonicity ("spasm") is associated with increased anodermal blood flow and improved rates of fissure healing. Topical calcium channel blockers and topical nitroglycerine also reduce sphincter tone, increase anodermal blood flow and encourage healing. Nitroglylcerine is less popular because of side effects (headache).

If the history is longer than a few weeks and the physical findings suggest chronicity (i.e., exposed sphincter muscle fibers, hypertrophied papilla, sentinel pile, and palpable induration), this conservative therapy may not help.

If symptoms warrant, a chronic fissure may be treated by Botox injection or by operation, generally by lateral internal sphincterotomy (LIS). Botox (a total of 20-50 units injected into the sphincter or inter-sphincteric plane) transiently reduces sphincter tone. Success rates are variable, probably in the range of 50-60%, and the procedure is safe. LIS relieves the internal anal sphincter hypertonicity ("spasm") and allows the fissure to heal in over 90% of cases. Minor disturbances of continence, especially for flatus, may complicate LIS; the exact rate of diminished continence is controversial but may be as high as 30%.

3.3. Fistula-Abscess Disease

Anorectal abscess and fistula are the acute and chronic phases, respectively, of the same disease. The disease begins as an infection in the anal glands, and initially presents as an abscess. When the abscess is surgically drained, or drains spontaneously, a communication (i.e., a fistula) exists between the anal gland of origin and the perianal skin.

The infection begins in the intersphincteric plane, where many of the anal glands terminate. The infectious process may remain in this plane as an intersphincteric abscess, or, more commonly, it may track downward in the intersphincteric plane to present as a perianal abscess. Similarly, infection may penetrate the EAS to enter the ischiorectal fossa. Many complex variations are seen, and these variations are determined by the direction of spread of the abscess and sometimes by inappropriate intervention. The infection may track circumferentially from one side of the anal canal to the other to cause a "horseshoe" abscess. Perianal and ischiorectal abscesses account for at least three-quarters of anorectal abscesses.

The classical signs of inflammation are generally present, although with an intersphincteric abscess there may be nothing to see. In the case of intersphincteric abscess, the patient will be too tender for adequate examination, and examination under anesthesia will be necessary.

Management of the abscess consists of incision and drainage, and this can usually be accomplished under local anesthesia. To ensure adequate drainage, a cruciate or elliptical incision is made. For the one-half to two-thirds of patients who go on to develop a fistula in ano, a fistulotomy, or laying-open, with curettage of the track is required. The wound heals secondarily. Nonhealing or recurrence of the fistula usually indicates a failure to destroy the gland of origin. In performing fistulotomy, the utmost attention must be paid to the anatomic relationship between the fistula track and the sphincter mechanism. Excessive division of muscle contained within the fistula can lead to partial or complete fecal incontinence.

3.4. Pilonidal Disease

This is an acquired condition related to hair follicles in the natal cleft. Skin openings form in the midline (primary pits), from which abscesses and secondary tracks and openings may form.

Pilonidal disease is mainly seen in young, hirsute males. It commonly presents as an acute abscess, but may also present as a chronic "sinus," usually with multiple openings. The abscess stage of pilonidal disease is treated by incision and drainage, usually under local anesthesia. A midline wound in the natal cleft should be avoided, if possible. After the abscess has healed, some of these patients will require definitive surgery to deal with the primary and secondary tracks. The optimal treatment is very controversial; a simple and effective method consists of opening the anterior wall of the tracks and suturing the edge of the track to the skin edge. This technique is called "marsupialization."

Chapter 15: Acute Viral Hepatitis

M. Ma

1. Introduction

The term acute hepatitis refers to recent, sudden injury to the liver. Acute hepatitis is usually a self-limited disease. Some patients however rapidly progress to fulminant liver failure, or the disease gradually evolves into chronic hepatitis with inflammation persisting beyond six months. Viral infection is amongst the commonest causes of acute hepatitis (Table 1).

Table 1. Causes of acute hepatitis

- ➢ Viruses
  - ○ Hepatitis A
  - ○ Hepatitis B
  - ○ Hepatitis C
  - ○ Hepatitis D
  - ○ Hepatitis E
  - ○ Herpes simplex
  - ○ Cytomegalovirus
  - ○ Epstein-Barr
  - ○ Adenoviruses
- ➢ Drugs and Toxins
- ➢ Alcohol
- ➢ Ischemia
- ➢ Wilson's disease
- ➢ Others

In North America, hepatitis A, B and C are the commonest causes of viral hepatitis (Table 2). Most acute viral hepatitis infections generally produce quite mild and non-specific symptoms. When the hepatitis is more profound, symptoms include malaise, fatigue, nausea, vomiting and low grade fever. Right upper quadrant abdomen discomfort is common and is due to hepatic swelling causing distension of the hepatic capsule. Marked abdomen pain is not a feature; when present, this warrants consideration of an "acute" abdominal process that should include surgical evaluation of the intra-abdominal contents, including the hepatobiliary system and the entire gastrointestinal tract. Patients with severe viral hepatitis might have clinical jaundice. Laboratory testing will show acute elevation of aminotransferases (AST and ALT); more severe cases may exhibit impaired hepatic synthetic function abnormalities including elevated bilirubin and INR. The mainstay of treatment is supportive care. The convalescent stage is usually 7 to 10 days, with the total illness lasting two to 6 weeks. An occasional case will progress to acute liver failure, requiring liver transplantation. It is important to provide post-exposure prophylaxis to close contacts and family members to avoid spreading the viral infection.

The key features of the different types of viral hepatitis are summarized in Tables 2 and 3.

Table 2. Overview of viral hepatitis

	Virus type	Transmission	Incubation (days)	Serologic diagnosis	Fulminant hepatitis	Chronicity
		Fecal/oral				
HAV	RNA	Fecal/oral	20-35	HAV-IgM	0.1-2.0%	No
HEV	RNA	Fecal/oral	10-50	Anti-HEV	1-2% 15-20% (pregnant)	No

	Virus type	Transmission	Incubation (days)	Serologic diagnosis	Fulminant hepatitis	Chronicity
			Percutaneous			
HBV	DNA	Percutaneous Venereal Perinatal (Asia)	60-110	HB$_s$Ag	0.1-0.5%	• Adults <5% • Preschoolers 25% • Neonates >90%
HCV	RNA	Percutaneous	35-70	Anti-HCV	<1%	> 80%
HDV	RNA	Percutaneous Venereal	60-110	Anti-HDV	1% especially addicts	• usual in superinfection • rare in co-infection

Table 3. Prevention and Treatment of Acute Viral Hepatitis

	Hepatitis A	Hepatitis B	Hepatitis C
➤ General	o Need for good sanitation and hygiene. o Hepatitis A infection confers life-long immunity. o Effective vaccine	o Vaccine synthesized from recombinant DNA o Minimal side effects o Confers protection from HDV	
➤ Indications for vaccination	o Occupational exposure (day care workers, military personnel, healthcare professionals, sewage workers) o Men who have sex with men(*) o Institutionalized o Residents and health care staff at chronic care facilities o Travellers to endemic areas o IVDU o Children ≥ 2 years of age in communities with high rates of Hep A o Chronic liver disease	**Universal vaccination in Canada**	No vaccine

	Hepatitis A	Hepatitis B	Hepatitis C
➤ Prophylaxis on exposure	**All household and sexual contacts** o Immune serum globulin 0.02 mL/kg IM if within 2 weeks of exposure o No treatment for casual school or work contacts unless epidemic of HAV identified	**Needle stick, sexual and household contacts** - If seronegative, administer HBIG and start Hep B vaccine series within 12 hours of exposure **Perinatal** o Routine pre-natal screening with HB$_s$Ag o Within 24-48 hours of delivery, administer HBIG and start Hep B vaccine series o Consider oral antiviral therapy in expecting mothers who have very high HBV DNA	**Needle stick** o Test for HCV-RNA, AST, bilirubin at baseline, 4 and 12 weeks – if positive, treat with PEG-IFN and Ribavirin **Perinatal** o Rare transmission-more likely if mother is immunosuppressed o Test infant with HCV RNA **Sexual transmission** o Rare o Condoms advised for multiple sex partners
➤ Treatment	o Supportive care. Most cases resolve spontaneously. Hospitalization rarely needed. o Prophylaxis and prevention of secondary spread is perhaps the most important aspect of treatment. o *Activity* – Symptom-guided return to work; no activity limitations. o *Diet* – fatty foods poorly tolerated, exclude ethanol--no other restrictions. o *Drugs* – no role for corticosteroids (may increase the risk of a chronic carrier state); avoid sedatives, tranquillizers		o Supportive care o If patient hasn't spontaneously cleared virus at 12 weeks. Start antiviral therapy. (Studies with IFN monotherapy only).

2. Hepatitis A Virus *(HAV)*
2.1. Epidemiology and Risk Factors

Previously termed "infectious hepatitis", hepatitis A virus (HAV) is an RNA virus that belongs to the enterovirus family. This enteric viral infection is a common disease worldwide and tends to cause mild self-limited illness. Severe hepatitis and liver failure are rare. Transmission is via the fecal-oral route: poor public hygiene in many developing countries and in other settings, sexual and household contacts. The anti-HAV IgG can be detected in 90% of the population in developing countries and in 30-40% of the population in developed countries.

Food and water contamination may lead to epidemic outbreaks. Given the globalization of food distribution and tourism, HAV is no longer just a disease of developing countries, and outbreaks have occurred in developed countries. Recent North American outbreaks have been associated with the ingestion of contaminated strawberries imported from developed countries and of raw clams and oysters from polluted water. Person-to-person spread results in sporadic cases. The hepatitis A virus is present in the stool of patients during the prodrome or pre-icteric phase until about two weeks after the onset of jaundice. Parenteral transmission is also possible, especially in intravenous drug users, but is much less common. Travelers to endemic areas, children in daycare, health care professionals and homosexual males are at increased risk of contracting Hepatitis A.

2.2. Clinical Course and Treatment

HAV is transmitted by the fecal-oral route. In developing countries, the infection occurs in childhood so that most children have experienced exposure to the virus. HAV infection during childhood has very mild symptoms and results in lifelong immunity. In developed countries with good sanitation, "population immunity" to hepatitis A infection is low in children and young adults. Few therefore are exposed to the virus during childhood. As increased symptom severity correlates with older age, when hepatitis A infection does occur, these adults tend to be symptomatic.

The infection usually causes mild to moderate acute hepatitis in adults. The incubation period is approximately 4 weeks and the acute illness lasts 2 to 3 weeks. The virus is present in the stool of patients from the prodromal or pre-icteric phase to about two weeks after the onset of jaundice (Figure 1). Person to person, oral-fecal spread can occur during this time. There is a brief period of viremia during the acute phase of infection, and thus parenteral transmission can occur in intravenous drug users sharing needles during this phase. During acute infection, patients have flu-like symptoms such as malaise, fatigue, anorexia, and fever. Mild to moderate jaundice usually is evident. There may be a cholestatic presentation with intense pruritus and jaundice. The liver enzymes ALT and AST are moderately elevated. In addition, there may be relapsing (biphasic) hepatitis.

Fulminant liver failure causing death or requiring liver transplantation has occurred infrequently: in the elderly and in those with underlying chronic liver disease. The advent of fulminant liver failure necessitates hospital admission for supportive care and preparation for liver transplantation. The mortality rate, usually from fulminant hepatitis, is very low (0.1%); rarely is liver transplantation required. Recovery follows acute hepatitis and patients develop lifelong immunity to HAV. There is no evidence for a chronic carrier state or the development of chronic liver disease.

2.3. Diagnosis

Both IgM and IgG antibodies to the virus (anti-HAV) are detectable in hepatitis A infection. The presence of an elevated IgM antibody indicates recent infection; this clinical test diagnoses an acute infection. The IgM response usually becomes undetectable at 6 months, but the IgG response persists for life and provides lifelong immunity against the virus (Figure 1).
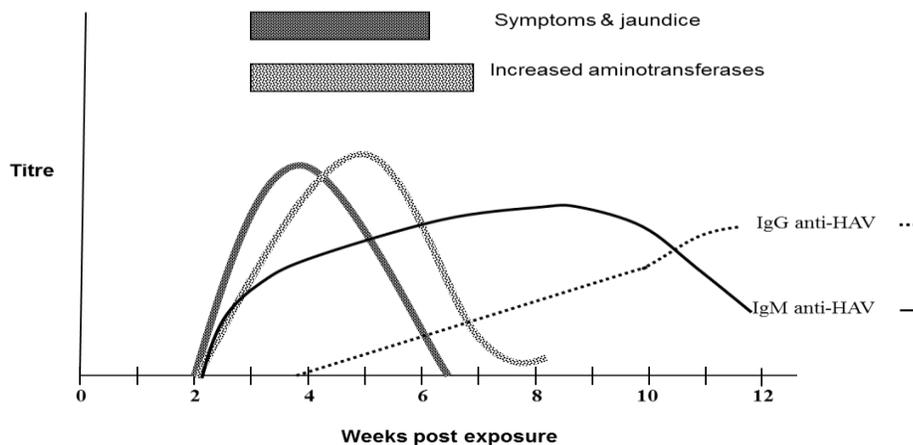
Figure 1. Clinical and serological course of infection with acute hepatitis A virus

2.4. Treatment

The illness is usually self-limited and there is no specific anti-viral therapy for acute hepatitis A. Management is therefore supportive. Patients can maintain their routine activities; strict bed rest is not necessary. Strenuous exercise has not been associated with adverse outcome during mild to moderately acute HAV infection. Diet can be liberal, encouraging a high calorie intake but excluding alcohol. Fatty foods are poorly tolerated and are best avoided. All unnecessary drugs, especially tranquilizers and sedatives, should be shunned. The patient's symptoms are the best guide for activity and return to work. Patient education helps alleviate anxiety. Referral to a specialist is not usually required.

2.5. Prevention

In the community, the prevention of hepatitis A is dependent on good sanitation and hygiene. At the time of outbreak, information regarding hygienic measures and immunoprophylaxis should be provided to family members or persons in close contact with the infected individual. This public health intervention is important to prevent the spread of hepatitis A infection. Two biologic agents can prevent disease: passive immunization with intramuscular polyclonal serum immune globulin and the hepatitis A vaccine.

Regular immune globulin preparation is effective in preventing hepatitis A, best used for passive immunoprophylaxis. The preparation consists of concentrated antibodies from pooled human plasma. The immune globulin has an efficacy of 80 to 90 percent when it is given before or immediately after exposure to HAV. Hence, it can be used for pre-exposure prophylaxis in travelers to endemic countries requiring short-term, immediate protection, and also in post-exposure prophylaxis of household and sexual contacts of an affected individual. The preparation is safe for short-term prophylaxis in children under the age of two and in pregnant women traveling to endemic areas. The current recommended dose of immune globulin is 0.02 mL/kg IM within 2 weeks of exposure.

Hepatitis A vaccines contain either purified, formalin-inactivated vaccine or live attenuated virus. These vaccines are safe and effectively provide immunity against hepatitis A virus. Administered in two doses, the current vaccines are recommended in patients above the

age of two who are inhabitants of communities with high rates of hepatitis A, are at risk of occupational exposure, or are traveling to endemic countries. Intravenous drug users (IVDU), those living in institutions, or those with chronic liver disease or hemophilia should also be vaccinated (Table 3). Because of the high efficacy of the vaccine, post-treatment testing for the development of antibodies is not routinely required. Although the vaccine is very safe, there are no data regarding the safety of the vaccines in children less than 2 years of age, or in pregnant women. The most common side effect of vaccination is pain at the site of injection (18-39%). The vaccine and immunoglobulins can be given together for post-exposure prophylaxis. In this situation, there is some inhibition of antibody production, but the titre of anti-HAV is more than adequate to prevent hepatitis A infection.

3. Hepatitis B Virus (*HBV*)
3.1. Epidemiology and Risk Factors

HBV is a unique DNA virus that replicates through reverse transcription of its mRNA. It behaves more like a retrovirus than a DNA virus. It accounts for 40% of acute viral hepatitis in the U.S. In North America, HBV infection occurs primarily in adolescents and adults because of sexual activity and intravenous drug use (Table 4). In endemic countries, HBV infection occurs in infants and children through maternal newborn transmission or child-to-child transmission by contaminated vaccination needles or other means. This vertical transmission of HBV from mother to newborn results in the vast majority of chronic carriers worldwide. Hepatitis B infection from blood transfusion has decreased dramatically since the implementation of routine screening and the use of volunteer blood donors. Nevertheless, HBV infection through blood transfusion is still represents a high risk at 1 per 72,000 units transfused in comparison to other blood borne viruses (Table 5).

Table 4. Risk factors associated with reported cases of acute HBV in the U.S.

Risk factors	Percentage (%)
➢ Heterosexual activity	48
➢ IV Drug use	11
➢ Homosexual activity	7
➢ Health-care employment	2
➢ Household contact	1
➢ Transfusion, dialysis	1
➢ Unknown	30

Source: Data from Centers for Disease Control and Prevention, 1992

Table 5. Risk of Transfusion Transmitted Infection

➢ Hepatitis B	1/72,000
➢ Hepatitis C	1/3 million
➢ HIV	1/10 million
➢ HTLV	1/1.1 million

Source: Database from CMAJ – Canadian Blood Services 1990-2000

3.2. Clinical Course

HBV is a highly contagious virus. Percutaneous or mucous membrane exposure to infectious blood or body fluid can lead to acute infection in any person lacking immunity against the virus. The infectivity of the blood or body fluid correlates to the concentration HBV DNA or the presence of HB_eAg. The higher the HBV DNA concentration in blood or fluids, the greater is the risk of transmission. The incubation period ranges from 60-110 days. The clinical presentation of acute hepatitis B ranges from subclinical to the rare case of fulminant hepatitis (0.1-0.5%). Clinical jaundice develops in approximately 30% of patients at presentation. Relapsing (biphasic) hepatitis is uncommon. From 5% to 10% of persons with HBV will experience a serum-sickness-like syndrome (immune complex disease) characterized by skin rash, angioedema and arthritis. The outcome of HBV infection is frequently age-dependent. Perinatal transmission is associated with a 90% likelihood of chronic infection. Conversely, when acquired as an adult, HBV infection is usually self-limited; less than 5% progress to chronic hepatitis (persistent presence of HBV after 6 months of infection). Lower rates of viral clearance occur in immune-compromised persons.

3.3. Diagnosis

The clinical course of acute HBV infection, appearance and clearance of viral antigens, and host immune response are shown in Figure 2. The components of the HBV virus help clarify the multiple serological tests that evaluate HBV infection (Table 6A). The hepatitis B virus consists of a 28 nm central core containing the genome (a single molecule of partially double-stranded DNA) and a specific DNA polymerase. Hepatitis B core antigen (HBcAg) is an intracellular antigen that is expressed in infected hepatocytes, but is not detectable in serum. This core antigen is structurally distinct from the surface antigen (HB_sAg), which packages the core in the cytoplasm of the hepatocyte. HB_sAg appears in serum and represents the serologic hallmark of HBV infection. Hepatitis B_e antigen (HB_eAg), another viral antigen, is a secretory protein, a subunit of HB_cAg that is processed from the precore protein. Released into the serum, HB_eAg is a general marker for HBV replication and infectivity. HB_eAg positivity thus implies viral replication, and is an indicator of high infectivity. There are also viral mutants that do not produce HB_eAg; these "pre-core mutants" as a cause of severe acute hepatitis would not be evident by HB_eAg. The HBV DNA is the most sensitive marker for detecting the presence of the virus. The HBV DNA as a routine test will clarify the viral replication status, guide therapy in patients with chronic hepatitis B, detect pre-core mutant virus, assess treatment response, and monitor the development of treatment-resistant HBV.

Table 6A. Interpretation of hepatitis B markers

Marker	Interpretation
➤ HB_sAg	o HBV infection; may be acute or chronic
➤ HB_sAb	o Immune to HBV (as natural immunity or after HBV vaccination)
➤ HB_cAb-IgM	o Acute HBV infection (newer and more sensitive assays may also be positive during reactivation of chronic infections)
➤ HB_eAg	o High infectivity/viral replication (precore mutant viruses lack HBeAg)
➤ HB_eAb	o Low or no infectivity, or precore mutant virus infection
➤ HBV-DNA	o Measure of infectivity or replicative state.
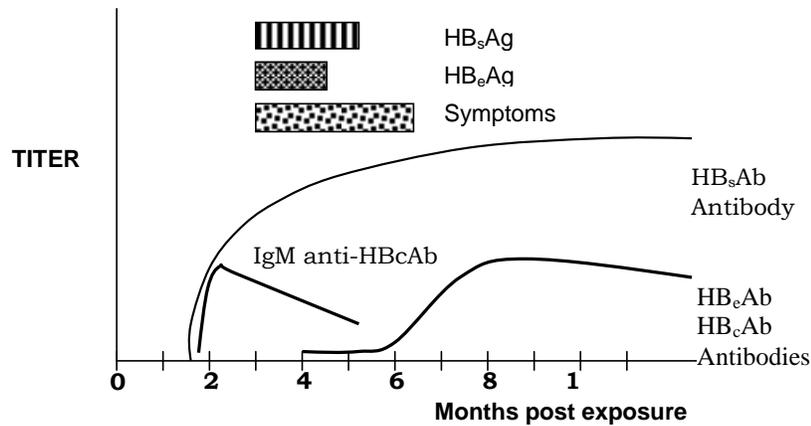
Figure 2. Typical clinical and serologic features of acute hepatitis B infection.

Acute infection becomes evident by the appearance of HB$_s$Ag, HB$_e$Ag and HBV DNA in the circuation, beginning in the preclinical phase. IgM anti-HB$_c$ (hepatitis B core antigen) soon follows, early in the clinical phase. Hence, presence of this IgM anti-HB$_c$ antibody plus HB$_s$Ag provides the diagnosis of acute HBV infection. With resolution of the acute infection, serum ALT falls to normal, HB$_s$Ag clears, seroconversion develops and certain antibodies arise: HB$_s$Ab (as HB$_s$Ag disappears), anti-HB$_c$ (IgM switches to IgG), and HB$_e$Ab (replacing HB$_e$Ag). HBV DNA disappears. IgM anti-HBc however can recur in HBV carriers who have a flare of hepatitis. Only the persistence of anti-HB$_s$ and IgG anti-HB$_c$ indicate a prior HBV infection.

In chronic infection, HB$_s$Ag, HB$_e$Ag (for at least 6 months), and HBV DNA persist in blood. There is no recovery, normalization of ALT and no seroconversion. Anti-HBs does become evident although ~20% may experience a non-neutralizing form of anti-HB$_s$.

The significance of HBV markers and their importance in the interpretation are summarized in Table 6B.

Table 6B. Seromarkers of HBV infection and vaccination

	Acute Infection	Chronic infection			Previous infection	Vaccination
		Active (eAg +ve)	Inactive (eAg +ve)	Pre-core mutant (eAg –ve)		
➢ HB$_s$Ag	+	+	+	+	-	-
➢ Anti-HB$_s$	-	-	-	-	+	+
➢ IgM anti-HB$_c$	+	-/+	-	-	-	-
➢ IgG anti-HB$_c$	-	+	+	+	+	-
➢ HB$_e$Ag	+	+	-	-	-	-
➢ Anti-HB$_e$	-	-	+	+	+/-	-
➢ HBV DNA	+	+	-/low	+	-	-

3.4. Treatment

For acute hepatitis B infection in adults, supportive care suffices. There is no need for antiviral therapy. Most acute infections clear completely and patients develop immunity against the virus. The rare occurrence of fulminant liver failure requires intensive support and consideration for liver transplantation. For the < 5% of HBV-infected persons who develop chronic hepatitis B infection, anti-viral agenta employing pegylated interferon or oral nucleosides/nucleotides (like Lamivudine, Entecavir, Telbivudine, Emtricitabine, Adefovir, Tenfovir) are important to prevent the progression of disease to cirrhosis and liver failure. These generally are indicated in those with: acute liver failure, cirrhosis with clinical complications, cirrhosis (or advanced fibrosis) with a high serum HBV DNA, or reactivation of chronic HBV following chemotherapy or immunosuppression.

3.5. Prevention

Active immunization against the HBV is available. It has successfully changed the epidemiology of HBV infection in many parts of the world. The hepatitis B vaccine contains HBsAg that is synthesized by recombinant DNA technology.

The commercially available vaccines are safe and effective. After completing a course of vaccination, 95–99% of immunocompetent individuals develop a high titer of anti-HB$_s$ the protective antibody that prevents HBV infection. The side effects are minimal. Many countries have a universal vaccination program for infants or children. Vaccination is recommended for high-risk groups such as health-care workers, homosexuals, intravenous drug users, family contacts of chronic carriers, chronic transfusion recipients, and renal dialysis patients. The eventual goal is to eliminate hepatitis B infection through a successful global vaccination program.

A specific immune globulin preparation from pooled plasma has a high titer of hepatitis B surface (anti-HB$_s$) antibody. This hepatitis B immune globulin (HBIG) can offer protection (passive immunization) against hepatitis B infection after exposure to the virus. Administration should occur within 12 hours following a clear-cut exposure, such as an inadvertent "needle-stick" injury or sexual contact. Frequently, the hepatitis B immune globulin is combined with HB$_s$Ag-containing vaccine.

Routine pre-natal screening with HBsAg is essential for identifying mothers with acute or chronic hepatitis B who can transmit the virus to their newborns. To prevent this vertical infection, HBIG and hepatitis B vaccine should be administered within 24 to 48 hours of delivery to neonates at risk. Unfortunately, mothers with the highest concentration of HBV DNA can still transmit the virus in spite of passive and active immunization of their neonates. Lamivudine and tenofovir are safe for expecting mothers with high HBV DNA levels, and can minimize vertical transmission of HBV.

4. Hepatitis C Virus *(HCV)*
4.1. Epidemiology and Risk Factors

Hepatitis C was discovered in 1989. A single-stranded RNA virus of less than 80 nm in diameter, HCV belongs to the flavivirus family. This virus exists as different genotypes; any effect of such viral factors on the natural history of attendant liver disease is uncertain. It has a worldwide distribution and is a significance cause of chronic hepatitis. In North America, the genotypes 1, 2 and 3 account for most of the infection. The prevalence of HCV infection ranges from 1% in the general population, to as high as 90% in hemophilia patients who have received

clotting factor concentrate. Though common (230,000 new cases each year in the 1980s in the US), HCV infection has fallen (incidence now about 19000 per year).

The principal mode of HCV transmission is parenteral, acquired though intravenous drug use or blood transfusions. Transfusion-related cases account for 10%, yet only 1 out of every 3 million units transfused now result in hepatitis C infection. (Table 5) Intravenous drug use is the main basis for hepatitis C infection in developed countries. The decline in HCV relates to improved screening of blood products and the concern over HIV that might have limited its spread via illicit drug use. Infection through sexual contact or mother-to-newborn (perinatal transmission) does occur, but the infectivity is low, in contrast to hepatitis B.

4.2. Clinical Course

The incubation period ranges from 5 to 10 weeks (mean 7 weeks). Acute hepatitis C commonly has a mild clinical course: most are anicteric. Those with symptoms are more likely to clear the virus. Because the acute illness can be very mild, detection of acute HCV infection is difficult. Chronic HCV infection develops in 70 to 80% of patients, who then have a significant risk of developing cirrhosis and chronic liver failure many years in the future.

Chronic hepatitis C is usually asymptomatic. Fatigue is the most frequent complaint followed by somewhat vague manifestations like nausea, anorexia, myalgia, arthralgia (some have immune complexes) and cognitive impairment.

4.3. Diagnosis

Serological tests for HCV either identify viral antibody (ELISA) or constitute molecular tests to detect the virus (HCV-RNA using polymerase chain reaction, termed PCR) and classify its genotype. The presence of anti-HCV antibody suggests viral exposure and is not a marker of immunity. The majority of patients exposed to HCV then become carriers of the virus. The presence of anti-HCV antibody however does not necessarily indicate chronic infection. The diagnosis of chronic hepatitis C infection requires detecting the virus with the PCR test.

The antibody test (ELISA, enzyme-linked immunosorbent assay) is the primary screening test. It identifies antibodies to the nonstructural as well as the structural epitopes of the virus. Being both sensitive and specific, this ELIZA test is very useful in identifying patients who had exposure to the hepatitis C virus. False-positive ELISA testing occurs with hypergammaglobulinemia. False negatives occur soon after acute hepatitis C onsets, and in association with immunosuppression or renal failure. HCV RNA PCR test is thus essential to clinch the diagnosis and assess the viral load. This information guides the management of chronic hepatitis C infection including the response to treatment. Genotypes assist in understanding the epidemiology, the natural course of HCV and importantly, the response to therapy.

4.4. Treatment

Acute hepatitis C infection may be clinically self-limited but commonly leads to chronic infection and liver damage. Once established, chronic HCV becomes difficult to treat. The goal of treatment in chronic HCV hepatitis seeks to eradicate the virus, best predicted by a sustained virologic response: absence of HCV-RNA 6 months after stopping treatment. A combination of antiviral agents is necessary: pegalated interferon plus ribavirin. Genotype 1, being the most difficult HCV to treat, requires the addition of a direct antiviral agent: a protease inhibitor like

telaprevir or boceprevir, boosting the response rate to 70-80%. These antiviral therapies are undergoing further evaluation.

Chronic hepatitis C requires surveillance for progression to cirrhosis, liver failure and the development of hepatocellular hepatoma.

4.5. Prevention

There is no vaccine or specific immunoglobulin available for HCV. The risk of sexual transmission is extremely low. In stable, monogamous relationships, the use of condoms is unnecessary.

5. Hepatitis D Virus *(HDV)*

5.1. Epidemiology and Risk Factors

The delta virus, HDV, is a small defective RNA virus that requires the presence of hepatitis B surface antigen for its expression; complete virion assembly and expression. The delta virus utilizes the HB_sAg protein as its external coat to attach to and enter hepatocytes. Found worldwide, HDV may represent a co-infection in some 5% of chronic HBV carriers in many developing countries. In North America, less than 1% of HB_sAg-positive patients have evidence of HDV infection, almost exclusively among intravenous drug abusers and their sexual partners. More common in the Mediterranean basin, 14-50% of HB_sAg-positive patients also harbor HDV in parts of Italy.

5.2. Clinical Course

Hepatitis D infection produces a spectrum of manifestations, from being asymptomatic to developing fulminant liver failure, as a super-infection in a person who is already a chronic HBV carrier. Super-infection tends to result in a more severe hepatitis than hepatitis B alone; further, 80% go on to chronic infection. Co-infection with both B and D viruses causes chronic hepatitis D infection in less than 5% of persons. Hepatitis D infection has the highest morbidity and mortality rate of all the hepatitis infections. The presentation is that of acute hepatitis or a flare of hepatitis, and the disease can rapidly evolve into cirrhosis, liver failure or hepatocellular carcinoma.

5.3. Diagnosis

The hepatitis D antigen (HDAg), associated with HDV, is detectable only during the early phases of the acute infection. The antibody to delta antigen (anti-HDV), providing the serologic marker for acute and chronic hepatitis D infection, in contrast appears late in the course of acute delta infection. Such timing would miss the HDV infection, and so might erroneously diagnose acute hepatitis B alone. The anti-HDV antibody disappears within months after hepatitis recovery. In chronic hepatitis D infection, the IgM anti-HD antibody and IgG anti-HD antibody persist. HDV-RNA, using reverse transcriptase-polymerase chain reaction (RT-PCR), detects the HDV genome indicating ongoing infection. Hence, the HDAG, anti-HDV and HDV-RNA assays will differentiate the 3 HDV-related clinical entities:
1. Acute HBV/HDV co-infection – serum HDAg appears early and then disappears; IgM anti-HDV appears early, then disappears, being replaced by IgG anti-HDV;
2. Acute HDV super-infection of a chronic HBV carrier (HB_sAg and IgM anti-HBc positive), and
3. Chronic HDV (and HBV) infection – HDV-RNA persists

5.4. Treatment

There is no proven treatment for acute co-infection of HDV and hepatitis B virus, or for super infection of HDV in the chronic hepatitis B carrier. Treatment is supportive for acute co-infection. If fulminant liver failure develops, consider liver transplantation.

5.5. Prevention

Persons who are at risk for HBV infection are also at risk for HDV infection. Hepatitis B vaccination protects against hepatitis D. Hepatitis B carriers should be counseled about avoiding high-risk behaviors in order to reduce becoming super-infected with HDV.

6. Hepatitis E Virus *(HEV)*

6.1. Epidemiology and Risk Factors

Hepatitis E virus, a single-stranded RNA virus, causes epidemic hepatitis, is enterically transmitted and thus shares many similarities with hepatitis A. HEV infections occur primarily associated with inadequate sanitation and represent a leading cause of acute viral hepatitis in developing countries. Domestic animals are a common reservoir for the hepatitis E virus; some surveys indicate infection rates exceeding 95% among domestic pigs in endemic countries. In women infected in the third trimester of pregnancy, however, HEV carries a high mortality rate (approaching 20%) When rarely seen in North America, it is almost exclusively in travelers returning from endemic regions.

6.2. Clinical Course

The clinical presentation is similar to HAV infection and is commonly mild. The incubation period is 10-50 days. The HEV infection causes self-limited hepatitis and the clinical course tends to be subclinical or mild. Following the incubation, some patients develop jaundice lasting 7 to 12 days. These patients may also experience malaise, fever, nausea, vomiting, anorexia, abdomen discomfort, headaches and fatigue. Liver transaminases may be elevated for 1 to 2 months. Chronic infection does not occur.

6.3. Diagnosis

The diagnosis of HEV comes from a history of travel or possible exposure to contaminated water or food, as well as the exclusion of HAV, HBV or HCV infection. Serological assay anti-HEV and polymerase chain detection assay are only available from reference laboratories.

6.4. Treatment

Treatment of active disease is supportive. It is not clear if acquisition of an acute infection will provide lifelong immunity.

6.5. Prevention

There is no passive immunoprophylaxis for HEV. Travelers going to endemic countries are at risk of contracting hepatitis E. The immune globulin produced in developed countries is ineffective to prevent HEV infection, because the preparation contains little or no anti-HEV antibody. It is not clear if the immune globulin from developing countries would be more effective. Travelers to endemic countries should be advised not to consume any uncooked food or untreated water. Safe practices, such as hand washing prior to eating and no swimming in

polluted water, would decrease the risk of contracting HEV. These recommendations are particularly important to the pregnant travelers because of the possibility of fulminant liver failure with HEV infection. An experimental vaccine based on recombinant viral proteins has been developed and tested in a population of military personnel working in a developing country. This vaccine appeared to be safe and effective. Unclear is if the vaccine offers long-term protection or is cost-effective for this generally mild disease.

7. Epstein-Barr virus (EBV) and Cytomegalovirus (CMV)

EBV and CMV are herpes viruses that can cause acute viral illness and hepatitis. EBV is widely dispersed. About 90-95% of the North American population is seropositive, most after subclinical infection. Symptomatic infections present with infectious mononucleosis characterized by fatigue, headache, pharyngitis, fever, posterior cervical chain adenopathy, splenomegaly and lymphocytosis. Mild hepatitis is a common presentation, but jaundice, hepatomegaly and severe hepatitis are rare presentations.

CMV infection in an immunocompetent host usually presents with asymptomatic elevation of serum transaminases ALT and AST. More severe CMV hepatic involvement is limited to those who are immunocompromised, such as persons with AIDS, and allograft organ recipients receiving anti-rejection therapy.

8. Other viruses

Other viruses that can cause liver injury (e.g. Herpes simplex and yellow fever) account for less than 1% of all acute viral hepatitis in North America. New hepatitis-causing viruses will likely be discovered in the future.

9. Complications of Acute Viral Hepatitis

Most patients with viral hepatitis recover completely. The most important complication is the development of chronicity, which may follow hepatitis B, C and D. Chronic hepatitis represents continued disease activity beyond 6 months. This complicates acute hepatitis B infrequently in adults but occurs in acute hepatitis C in over 70% of cases. Chronic hepatitis is suspect if symptoms and/or elevated serum aminotransferase levels persist beyond six months. Chronic hepatitis does not occur in hepatitis A or E.

9.1. Fulminant Liver Failure

Fulminant liver failure is the development of acute liver cell injury proceeding to liver failure and hepatic encephalopathy within 8 weeks in a patient without any known previous liver disease. Clinically, the patient deteriorates with development of deep jaundice, confusion and drowsiness. The encephalopathy can progress into deep coma. Because of massive liver necrosis, there is deficiency of clotting factors, and hence the INR/PT becomes progressively abnormal. At this stage, the mortality rate exceeds 50% unless a liver transplant can be performed rapidly. Death may occur from infection, hypoglycemia, increased intracranial pressure with cerebral edema, or renal failure. Massive hepatic necrosis leads to a shrunken liver in which the architecture collapses histologically. Despite this, regeneration can occur with histologic recovery. Usually a liver biopsy is not required; the procedure is associated with considerable bleeding risk unless done by the transjugular route.

9.2. Cholestasis

Occasionally, acute viral hepatitis exhibits a cholestatic phase, in which the patient becomes intensely pruritic and jaundiced. This occurs most commonly in hepatitis A. The enzyme pattern changes, with a fall in the serum aminotransferases but with an increased alkaline phosphatase and gamma-glutamyl transpeptidase (GGT). Biliary tract disease and drug toxicity must be excluded. Resolution within a few weeks is the usual course.

9.3. Relapsing (Biphasic) Hepatitis

Clinically, these patients begin improving, only to have a recurrence of the signs and symptoms of their hepatitis. Resolution is usually complete. This pattern is most characteristic of hepatitis A. In some cases of hepatitis B, the second phase is due to acute hepatitis D. Hepatitis C is characterized by repeated and wide fluctuations in liver aminotransferase values, but a true biphasic clinical course is uncommon.

9.4. Immune Complex Disease

Immune complex disease occurs with acute viral hepatitis. This is due to circulating immune complexes of viral proteins and antibody, with complement activation. Extrahepatic manifestations in acute hepatitis A are uncommon, but include arthritis, vasculitis, thrombocytopenia and aplastic anemia.

In both hepatitis B and C, about 5-10% of cases initially develop a serum-sickness-like syndrome characterized by skin rash, angioedema and arthritis. Other immunologic manifestations include pericarditis, aplastic anemia or neurologic abnormalities such as Guillain-Barre syndrome.

The extraintestinal manifestations associated with chronic hepatitis will be discussed in the next chapter.

10. Summary

Acute viral hepatitis is usually a self-limited disease and in most cases requires supportive care only. For the few patients who develop fulminant liver failure, liver transplantation will be the only treatment option. Chronic infection can develop in patients with HBV, HCV and HDV infection.
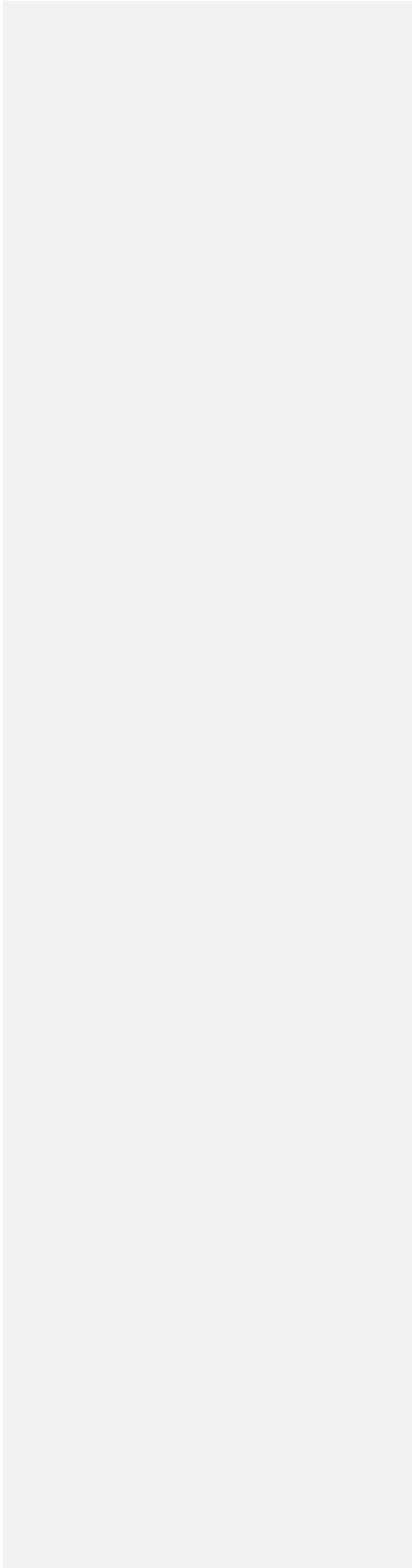
Chapter 16: Chronic Viral Hepatitis
S. Jayakumar and V. G. Bain

1. Introduction

The term chronic hepatitis means active, ongoing inflammation of the liver that persists for more than six months, being detected by biochemical and histologic means. It does not imply an etiology. The biochemical hallmark of chronic hepatitis is an increase in the serum aminotransferases (AST and ALT), with minimal elevation of the alkaline phosphatase (AP). When the hepatitis becomes severe and/or prolonged, hepatic dysfunction may become apparent with an increase in serum bilirubin, and prothrombin time/INR, and a decrease in serum albumin concentration. Typically, biochemical tests are used to identify and follow patients with chronic hepatitis. Liver biopsies serve to define more precisely the nature of the chronic hepatitis, and to provide useful information regarding the extent of damage and prognosis.

Histologically, chronic hepatitis is characterized by infiltration of the portal tracts by inflammatory cells. These cells are predominantly mononuclear, and include lymphocytes, monocytes and plasma cells. Liver biopsy is the gold standard to evaluate the grade (degree of inflammation) and stage (degree of fibrosis/cirrhosis) of chronic viral hepatitis. The most commonly used system for grading and staging of hepatitis is the METAVIR system established in France (Table 1). Histologic or inflammatory activity (A score) is determined by an algorithm incorporating the amount of portal and lobular inflammation and necrosis into a score from A0-A3. The degree of fibrosis (F score) is evaluated separately to obtain the stage of disease and ranges from F0-F4 (Figure 1-4). There are several other histologic scoring systems in use as well.

Table 1. The METAVIR system for staging/grading chronic hepatitis Histologic

A0 = no activity	F0 = no fibrosis
A1 = mild activity	F1 = portal fibrosis without septa
A2 = moderate activity	F2 = portal fibrosis with few septa
A3 = severe activity	F3 = numerous septa without cirrhosis
	F4 = cirrhosis

*determined by an algorithm incorporating degree of interface and lobular necrosis
Activity(A); Fibrosis (F)

The commonest cause of chronic hepatitis is a viral infection of the liver. Other causes include autoimmune hepatitis, drug-induced hepatitis, Wilson's disease, 1-antitrypsin deficiency, and steatohepatitis. Primary biliary cirrhosis and primary sclerosing cholangitis may occasionally mimic chronic hepatitis, but are not usually classified as such. Table 2 summarizes an approach to help determine the etiology of chronic hepatitis.

2. General Considerations

Only hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) cause chronic liver disease. HBV and HCV comprise the vast majority of these cases, with HDV infections occurring only in persons who have concurrent or pre-existing HBV infection. A careful assessment of risk factors is helpful in determining the cause of chronic hepatitis (Table 2).

The rate of transmission via needle stick injury varies with the type of virus exposure, bore size of the needle, and whether the needle is hollow or not (Table 3). In most cases, selected laboratory tests will provide confirmation of the diagnosis.
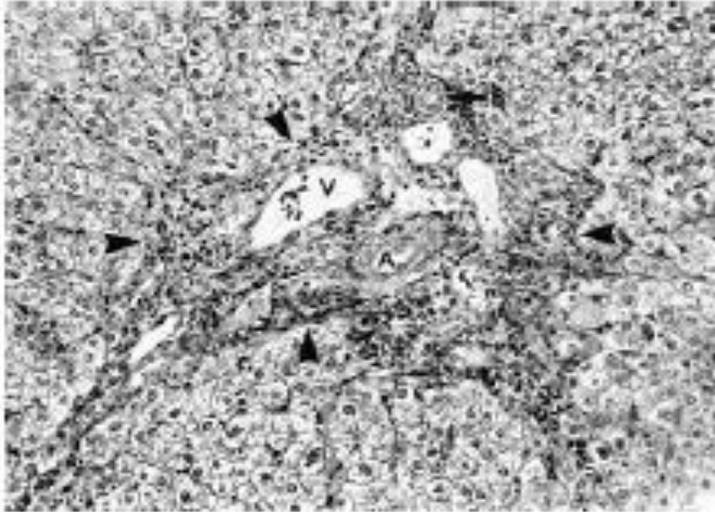
Figure 1. Mild chronic hepatitis. This portal tract contains a chronic inflammatory infiltrate that is confined to the portal triad and does not extend past the limiting plate (arrowheads).
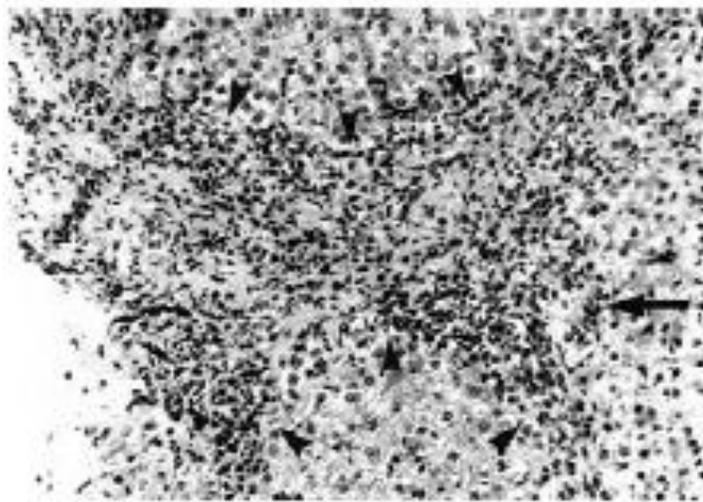
Figure 2. Moderately severe chronic hepatitis. Inflammatory cells are shown infiltrating and destroying the periportal hepatocytes (arrow) and disrupting the limiting plate (interface necrosis) (arrowheads).
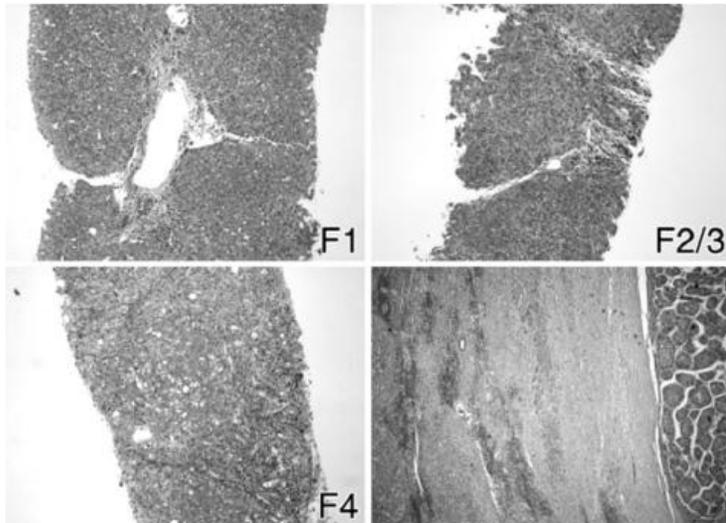
Figure 3. METAVIR staging system. F1= Minimal fibrosis without bridging; F2/3= Bridging fibrosis in which fibrous tissue connects the joining triads; F4= Cirrhosis. The slide on the bottom right represents chronic hepatitis and a hepatocellular carcinoma.
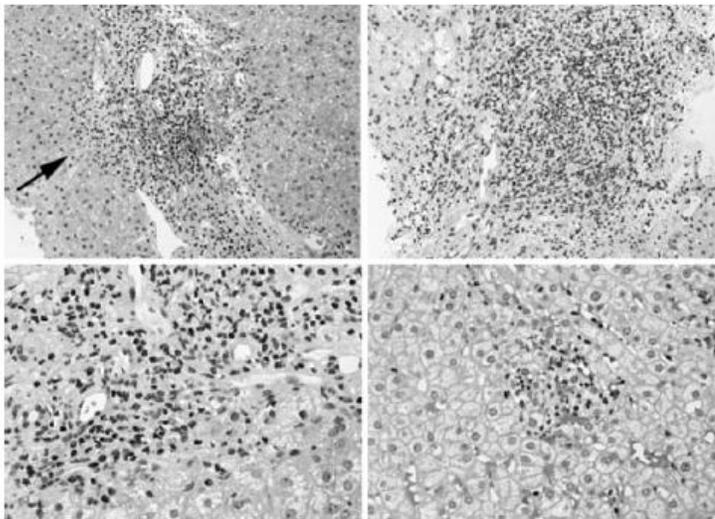
Figure 4. METAVIR grading system. The histologic activity is dependent primarily on the degree of interface necrosis but lobular necroinflammatory foci are also included in grading. Mild interface necrosis (arrow) is evident in the top left slide. A high-powered view below it demonstrates apoptotic bodies. On the top right, circumferential interface necrosis is seen. The high-powered view below it demonstrates a lobular necroinflammatory focus.

Table 2. Role of history and lab tests in the diagnosis of chronic hepatitis

Etiology	Key Points in History	Useful Lab Tests
➢ HBV	o Sexual history (homosexuality, use of prostitutes, promiscuity) o Family History o Country of origin o Intravenous/intranasal drug use (IVDU/INDU)	o HB_sAg – if positive, measure HB_eAg, HB_eAb and HBV DNA
➢ HCV	o Blood transfusion (pre-1990), Hemophilia o IVDU/INDU o Tattoos; piercings o HCV positive partner o Incarceration	o Anti-HCV o HCV RNA
➢ Drug Induced Hepatitis	o Careful history of all drugs and herbs (commonly isoniazid, nitrofurantoin, NSAIDs, and antibiotics)	o Liver biopsy (although not very helpful on its own)
➢ Wilson Disease	o Family history o Neurologic or psychiatric symptoms in children or young adults	o Serum ceruloplasmin o 24 hr urinary copper o Penicillamine challenge o Liver biopsy with hepatic copper concentration
➢ Alpha-1 Antitrypsin Deficiency	o Family history of liver or lung disease (COPD)	o Alpha-1-antitrypsin levels o Pi genetic testing
➢ Non-alcoholic Steatohepatitis (NASH)	o Obesity o Recent sudden weight gain/loss o Diabetes mellitus o Use of corticosteroids o Bariatric surgery	o Oral glucose tolerance test o HbA1c o Serum cholesterol profile (especially triglycerides) o Abdominal ultrasound

Table 3. Rate of Transmission of Viruses with Needlestick Injury

Virus	Rate of Transmission	Viral Particles/mL of Serum/Plasma
➢ Hepatitis B	30% (2-40%)	10^2-10^8
➢ Hepatitis C	3% (3-10%)	10^0-10^6
➢ HIV	0.3% (0.2-0.5%)	10^0-10^3

(Source: *NEJM 1995;:332 (7): 444-51*)

The clinical presentation of chronic hepatitis can include no symptoms, unexplained fatigue, or complications of cirrhosis including ascites, variceal bleeding and encephalopathy.

General treatment considerations include counseling about reducing the risk of transmission, vaccination for hepatitis A and B if a patient is seronegative, and vaccination for pneumococcus and influenza in the presence of cirrhosis. Persons are screened for complications of chronic liver disease and co-existing causes of liver dysfunction. Complete abstinence or minimal alcohol intake is advised, because of the risk of accelerated progression of viral hepatitis in the person who consumes a hepatotoxin such as alcohol.

3. Hepatitis B Virus (HBV)

3.1. Evolution to chronic liver disease

A number of factors determine whether an individual will clear an acute HBV infection or progress to a chronic carrier state: the age at infection is most important. Carrier rates in vertically infected newborns are greater than 90%, as compared to less than 1% in adult-acquired infection. Statistics Canada estimates that there are approximately 600,000 persons in Canada infected with Hepatitis B, with the majority of infections occurring in immigrants (6% rate of infection in "new Canadians," 1% in Canadian born individuals, and 4% rate of infection in First Nation Canadians). Untreated chronic HBV has a liver-related mortality of 20-25%.The immunologic status of the host is also important, as immunocompromised individuals (e.g., HIV, renal failure, post-transplant) are more likely to become chronic carriers. The severity of the acute disease also correlates with outcome. In general, the milder the acute illness, the more likely that progression to chronic liver disease will occur. Presumably, individuals with mild acute disease are those with a suboptimal immunologic response to the virus, whereas persons with more severe acute disease are manifesting a prompt and effective immunologic attack on hepatocytes harbouring HBV.

The rates of progression from chronic hepatitis B infection to cirrhosis, and cirrhosis to decompensation and hepatocellular carcinoma (HCC) are given in Table 4. Table 5 lists the risk factors for the development of HCC in patients infected with HBV.

Table 4. Rates of Progression over 5 years in HBV infection.

➢ Chronic HBV to cirrhosis (HBeAg positive)	17%
➢ Chronic HBV to cirrhosis (anti-HBe positive)	38%
➢ Compensated Cirrhosis to Decompensated Cirrhosis	15%
➢ Compensated Cirrhosis to HCC	10-17%
➢ Death in cirrhotics	15%

(Source: *Fattovich, J Hepatol 2008;48:336-352*)

Table 5. Risk factors for the development of HCC with chronic HBV

- ➢ HBV DNA level
- ➢ Level of fibrosis on liver biopsy
- ➢ Active inflammation on liver biopsy
- ➢ Age>45
- ➢ Male
- ➢ Increased ALT
- ➢ Family history of HCC
- ➢ Africans > Asians >> Caucasians
- ➢ Both cirrhotic and non-cirrhotic patients are at risk

3.2. Hepatitis B genotypes

There are currently 8 different HBV genotypes, based upon variations in the HBV genome sequence. The different geographic distributions of the genotypes are listed in Table 6. Although different genotypes may play a role in altered natural history, disease activity and treatment efficacy, genotype testing is just beginning to have a role in treatment considerations.

Table 6. Geographic Distribution of Hepatitis B Virus Genotypes.

Genotype	Geographic Range
A	North America, Europe, Africa
B,C	East Asia, North America
D	Worldwide Distribution
E	Africa
F	South America, Alaska
G	North America
H	Central America

3.3. Hepatitis B mutations

HBV is prone to the development of mutations because of the lack of proofreading function of reverse transcriptase. Pre-core variants are encountered most frequently. The pre-core region of HBV codes for HBeAg. A mutation in the pre-core region creates a premature stop codon, so that HBeAg cannot be produced. Clinically, this presents as chronic HBeAg negative hepatitis. The patient has ongoing inflammation as suggested by elevated transaminases, as well as viremia with detectable HBV DNA in the absence of HBeAg. This mutation is associated with genotypes B and D, and found most commonly in Mediterranean countries and in Asia.

A comparison between HB_eAg positive and negative cases is presented in Table 7. Clinically, confusion may arise in distinguishing an inactive hepatitis B carrier from HB_eAg negative chronic hepatitis. HB_eAg negative chronic hepatitis is suggested by features of active inflammation (elevated ALT, biopsy demonstrating active inflammation) and the presence of viral replication (HBV-DNA > 2000 IU/mL). Other causes of coincidental hepatitis (e.g.; drugs, HDV) must also be excluded.

Table 7. Comparison of HBeAg positive and HBeAg negative chronic hepatitis

Etiology	HB$_e$Ag positive	HB$_e$Ag negative
➢ Epidemiology	o Most common type in North America	o Higher incidence in Asia, Europe, and other Mediterranean countries
➢ Natural history	o Lower rate of progression to cirrhosis	o Higher rate of progression to cirrhosis
➢ Treatment	o Seroconversion to anti-HBe associated with long term viral suppression	o viral recurrence usual after treatment course
➢ Monitoring of treatment response	o Monitoring of HBeAg seroconversion to anti-HBe positive o Normalization of liver enzymes o Marked reduction in HBV DNA	o Normalization of liver enzymes o Marked reduction in HBV DNA

3.4. Presentation

The majority of persons with chronic hepatitis B are asymptomatic or have only mild fatigue. They might give a history of parenteral exposure to blood or blood products, unprotected sex, or a family history of hepatitis B infection. Liver enzyme abnormalities, even when incidentally discovered, should raise the possibility of underlying viral infection. Screening of family and sexual contacts of known cases will often reveal additional cases. Uncommonly, HBV (as well as HCV) may present with extrahepatic manifestations (Table 8) secondary to circulating antigen-antibody immune complexes.

Table 8. Extrahepatic Manifestations of HBV and HCV by Organ System

Organ System	HBV	HCV
➢ General	o Serum sickness like syndrome (fever, skin rash, arthralgias, arthritis)	
➢ Renal	o Glomerulonephritis esp o membranous	o Glomerulonephritis esp membranoproliferative
➢ Vascular	o Polyarteritis nodosa o Polymyalgia Rheumatica	
➢ Hematological		o Cryoglobulinemia o Lymphoma o Monoclonal gammopathies
➢ Endocrine		o Diabetes Mellitus
➢ Dermatological	o Papular acrodermatitis	o Porphyria cutanea tarda o Leukocytoclastic vasculitis

3.5. Diagnosis

A summary of the interpretation of seromarkers of hepatitis B is provided in Table 9. The definition of chronic HBV requires positive HBsAg for greater than six months. There may be HB_eAg positive and HB_eAg negative disease. Viral markers are helpful to determine the phase of disease (Figure 5). HB_eAg and HBV-DNA in serum confirm active HBV replication. When HBV-DNA is > 20,000 IU/mL (note this value for HB_eAg negative cases is 2000 IU/ml), there is a high viral load, indicating a high degree of infectivity (all physiologic fluids are potentially infectious). Although a negative HBV-DNA indicates very low or absent infectivity, the sensitive polymerase chain reaction (PCR) technique will still detect the virus. If HB_eAg is negative, there is usually lower infectivity, although as discussed this may represent a pre-core mutant. Core antibody serology is not usually required in the routine assessment of chronic hepatitis B (Table 5).

Table 9. Phases in the Course of Wild-Type Hepatitis B Infection

Phase	HBsAg	HBeAg	anti-HBe	ALT	HBV-DNA
➢ Immune Tolerant	+	+	-	N	↑↑↑↑
➢ Active Infection	+	+	-	↑↑↑	↑↑
➢ Seroconverion	+	-	+	N	<200 IU/mL
➢ Resolved Infection	-	-	+	N	negative

N: normal range

Adapted from: Sherman M, et al., *Management of Chronic HBV: Consensus Guidelines. Can J Gastroenterol. 2007 June; 21(Suppl C): 5C–24C*

3.6. Phases and Natural History

The first six months of HBV infection represent the acute hepatitis phase of the infection (Figure 5). This acute phase is not often seen in chronically infected adults who have contracted the virus at birth or in early childhood. Chronic hepatitis has three phases, termed the "replicative", "inflammatory" and "inactive" phases. As the replicative phase is most often observed after perinatal viral transmission, it is uncommon in Western countries. HBeAg and HBV-DNA are positive indicating high levels of HBV replication. Despite this, the aminotransferases are normal, or near normal and the liver biopsy is relatively inactive. For unknown reasons, patients may then enter the inflammatory phase in which their immune system now recognizes those hepatocytes harboring HBV, and begins to attack them. Accordingly, the aminotransferases become elevated and the biopsy shows chronic hepatitis, often of a severe degree. The level of viral replication as measured by the HBV-DNA will decline. If the patient successfully clears HBV, they will enter an inactive phase characterized by normalization of the aminotransferases and relative inactivity on the liver biopsy. HB_eAg will clear and anti-HB_e will form (seroconversion).
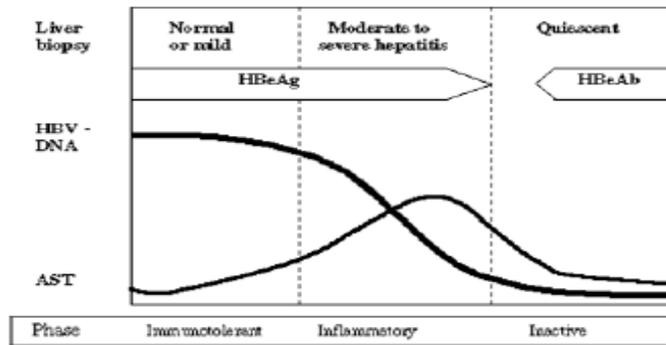
Figure 5. Phases of Chronic Hepatitis B

Seroconversion is associated with histologic and biochemical remission in most persons. Predictors of seroconversion are a high ALT, low HBV DNA titres, age less than 40, and the absence of cirrhosis. Spontaneous seroconversion occurs in 10-15% of persons per year. This number is reduced in perinatally acquired infection. HB_eAg negative patients (i.e., pre-core mutants) do not meet criteria for eAg seroconversion, as they are eAg negative at baseline. Patients who have converted their HB_eAg and have a negative viral load may still have HB_sAg for many years after they clear the HBV.

The natural history of hepatitis B is outlined in Table 9. Patients are at variable risk of developing cirrhosis and hepatocellular carcinoma (HCC):

a) Cirrhosis - The severity and duration of the inflammatory phase of HBV is one of the main factors that determine whether a patient will develop cirrhosis. The progression of chronic hepatitis to cirrhosis occurs in 20 - 30% of all chronic hepatitis B patients. Progression is more likely in those with replicative HBeAg negative pre-core mutant than in those with HB_eAg positive chronic hepatitis.

b) Hepatocellular cancer - Although patients with cirrhosis are at the highest risk of developing HCC, non-cirrhotic HB_sAg carriers patients are also at risk (see Table 5 for other high risk predictors). The risk of HCC in HBV chronically infected patients is 100 times higher than that for non-carriers. The five year rate of progression of compensated cirrhosis to HCC is estimated at 6-15%.

Surveillance for HCC in chronic carriers requires performing a serum α-fetoprotein and more importantly, an abdominal ultrasound, every six to 12 months.

3.7. Treatment Indications

The workup for chronic HBV patients prior to treatment is summarized in Table 10. Factors which must be taken into account when considering initiating treatment of HBV are HB_eAg status, viral load, patient age, and evidence of hepatic damage from the virus (Canadian Consensus Guidelines). Hepatic damage may be implied from elevated liver enzymes (indicative of ongoing inflammation), or histologic or radiographic evidence of fibrosis/cirrhosis. The HB_eAg status affects the accepted level of viral load, above which treatment should be considered; in patients who are HB_eAg positive, this level is >20,000IU/mL. In those who are HB_eAg negative, this level is >2,000IU/mL. Any evidence of fibrosis increases the likely need for treatment. Similarly, any patient with evidence of hepatic decompensation should be considered for initiation of treatment. In the latter group, both lamivudine and adefovir reduce the need for liver transplantation, and should be initiated.

Table 10. Laboratory assessment prior to therapy

Hepatitis B	Hepatitis C
o ALT, AST, ALP, Bilirubin, Albumin, PT/INR	o ALT, AST, ALP, Bilirubin, Albumin, PT/INR
o CBC, Electrolytes, Cr, glucose, TSH	o CBC, Electrolytes, Cr, glucose, TSH anti-HCV, HCV genotyping
o HBsAg, HBeAg, anti-HBeAg, HIV	
o serum HBV DNA titres	o Serum HCV RNA levels
o anti HDV (if risk factors or unexplained ↑ ALT)	o TSH, ANA, ASMA, B-hCG
	o ECG if older than 50 yrs, or cardiac disease
o Consider liver Biopsy if raised ALT	
o Abdominal Ultrasound	o Liver Biopsy recommended but not mandatory
o Fundoscopy if >50 yrs or history of diabetes	o Abdominal Ultrasound or hypertension
o AFP (selected pts)	

Adapted from: *Sherman M, et al., Management of Chronic HBV and HCV: Consensus Guidelines Canadian J Gastroenterol 2007; June; 21(Suppl C): 5C–24C.*

If a patient does not meet criteria for treatment at the time of assessment (normal ALT or HBV DNA negative), their liver enzymes should be checked every six to 12 months. If elevated liver enzymes develop, HBV DNA should be checked to confirm reactivation. A complete virologic response is defined as the sustained loss of HBsAg. This occurs in a small minority of patients, and therefore other endpoints are used to define treatment success, i.e.; partial virologic response.

Seroconversion (HB$_e$Ag to HB$_e$Ab) correlates with improved long-term outcome including a reduced risk of liver decompensation and development of HCC. The durability of seroconversion may be lower in perinatally acquired HBV infection. In HB$_e$Ag negative persons, successful response to treatment is measured by a) normalization of AST and ALT, and b) HBV DNA becoming undetectable.

3.8. Treatment Medications

Interferon-α and nucleoside analogues are available to treat chronic hepatitis B. The advantages of interferon-α are that it has a finite treatment duration (24 weeks in HBeAg positive patients, 48 weeks in HBeAg negative patients), as well as a durable treatment response in HBeAg positive patients. However, it costs more, has more side effects than lamivudine and requires subcutaneous injection. Furthermore, interferon-α is less effective in patients with a viral load $> 10^7$, low ALT levels, males, patients older than 40 years, and in patients with cirrhosis.

Lamivudine is a nucleoside analogue with antiviral effects against HBV. Administered orally, it has less adverse effects than interferon-α, and may be used in patients with decompensated cirrhosis. The optimal treatment duration is unknown, although it is dependent

upon the HB$_e$Ag status; many patients will have recurrence of HBV infection when lamivudine is stopped. Unfortunately, long term use of lamivudine results in high rates of resistance mutations, approaching 70% at 4 years.

Adefovir is a phosphonate nucleotide analog of AMP that has anti-viral activity against HBV. It is not as potent as some of the newer medications discussed below for treatment of HBV, but it does have a higher generic barrier to resistance than lamivudine.

Entecavir is a selective guanosine analogue, and is one of the most potent inhibitors of HBV DNA replication of all the current medications used today. The side effect profile is similar to that of lamivudine, and is therefore well tolerated. In treatment naive patients, resistance rates are quite low (1% after 3 years of entecavir therapy), whereas resistance rates are much higher in patients with prior resistance to lamivudine (32% after three years of treatment with entecavir).

Telbivudine is a pyrimidine analogue which is more potent than lamivudine and therefore can be used in patients with high HBV DNA levels. It is less potent than entecavir or tenofovir.

Tenofovir is a purine analogue that was initially used as part of the treatment regimen for HIV, and is now used for treatment of chronic HBV, both in the setting of HBV-HIV coinfection as well as chronic HBV mono-infection. Tenofovir is much more potent that adefovir in suppression of HBV DNA. Resistance to tenofovir is rare, and when it occurs, it is attributed to noncompliance. Uncommon side effects include renal dysfunction and Fanconi syndrome. As the drug is excreted via the kidneys, patients with renal dysfunction need dose adjustment or preferably, use of a different anti-viral agent.

Drug efficacy and resistance profiles for the various drugs are listed in Table 11. Asians often have a poorer response, likely because most have perinatally acquired HBV infection with normal or minimally elevated transaminases. Since the development of resistance mutations have been associated with flares of hepatitis or hepatic decompensation, those drugs with the lowest rates of resistance are preferred in patients who have more advanced liver disease.

Table 11. Drugs Used in the Treatment of HBV - Efficacy and Resistance Levels

Drug	Efficacy	Resistance Level
➤ PEG-IFN	↑↑↑	Nil
➤ Lamivudine	↑	↑↑↑
➤ Adefovir	↑↑	↑↑
➤ Entecavir	↑↑↑↑	↑*
➤ Tenofovir	↑↑↑↑	Minimal
➤ Telbivudine	↑↑	↑↑

* Resistance rates are increased in patients with a history of lamivudine resistance.

Table 12 lists the patient factors that predict response to treatment.

Table 12. Factors predictive of a response to treatment of HBV infection

o   Low HBV-DNA level

o   Immunocompetent

o   Adult-acquired infection

o   Active liver disease - ALT > 5x upper limit of normal, active hepatitis on biopsy

o   Female

o   Absence of HDV or HIV co-infection HBeAg +ve

3.9. Prevention

Active immunization is important to prevent transmission of HBV infection from a chronic carrier to family and sexual contacts. Condoms should be used to prevent infection in persons with multiple sexual partners. The safety of the HBV vaccine is well established. Universal vaccination is recommended in Canada, either neonatally or as a pre-adolescent. The eventual goal of vaccination is total eradication of hepatitis B . On a global scale, there have been many barriers to this goal but its realization would have profoundly positive effects in many countries. Information regarding hepatitis B prophylaxis recommendations is found in the acute hepatitis chapter.

4. Hepatitis C Virus (HCV)

Chronic hepatitis C has become the most common cause of chronic hepatitis in most countries, including Canada. The identified cases of HCV may represent only the "tip of the iceberg," with most cases still undiagnosed. Many cases are identified after investigation of raised liver enzymes in asymptomatic individuals, or after screening of blood donors. Other persons with HCV infection present to physicians with fatigue, malaise, or less commonly, with manifestations of advanced liver disease, or extrahepatic manifestations of chronic hepatitis C (Table 8).

Treatment of HCV may result in improvement of selected extrahepatic manifestations.

4.1. HCV genotype

As a result of RNA mutations, HCV has evolved different genotypes over time. Six HCV genotypes and 50 subtypes have been identified. Genotype 1 is the most common in North America, accounting for approximately 75% of cases. Genotype 2 and 3 each account for 10-15%. Although genotype does not affect the severity of HCV infection or its progression, it has significant therapeutic implications.

4.2. Epidemiology

HCV infection can be transmitted by the same routes as HBV infection, but the majority of cases (60-70%) are related to intravenous drug abuse, and 10% of patients will have had a previous blood transfusion. Patients receiving blood products prior to 1990 are at highest risk. With current screening of blood donors, the risk of transmission of HCV with a blood transfusion is only one in 3 million units transfused. In the remaining persons a source of HCV infection is often difficult to find. Non-parenteral transmission through sexual or intimate contact and

maternal-infant exposure occur much less often than with HBV. Other factors associated with a low rate of viral transmission are needlestick injuries, and intranasal cocaine use.

4.3. Natural History

Anti-HCV serologic testing has revealed that 60-85% of patients with acute HCV will remain chronically infected. Of those with chronic hepatitis, as many as 20% will be cirrhotic by 25 years. Thereafter, an additional 1% per year develops cirrhosis. Accelerated progression of HCV to cirrhosis is seen in persons with heavy alcohol use, obesity, and co-infection with HIV or HBV. In those under 40 years of age, significantly lower (2-8%) rates of cirrhosis at 20 years.

Chronic hepatitis C is a risk factor for the development of HCC. The increased risk is mostly limited to patients with cirrhosis and is estimated at 1-4% per year after the development of cirrhosis. Risk factors for the development of HCC in the presence of HCV are listed in Table 13. The current screening practice is abdominal ultrasound and serum α-fetoprotein (AFP) every six to 12 months.

Table 13. Risk factors for the development of HCC with Hepatitis C Cirrhosis

- o Male
- o Age > 50 years
- o Hepatitis B co-infection
- o Heavy alcohol intake
- o *Risk significant only with cirrhosis

4.4. Treatment

The workup of a person with chronic HCV prior to therapy is summarized in Table 10. Before discussing the treatment of hepatitis C, one must understand various terminology used to interpret response to treatment (Table 14): RVR (rapid virological response), EVR (early virological response), SVR (sustained virological response), and EOT (end of treatment) response. EVR can be further categorized as either viremic or aviremic.

Table 14. Treatment Response Abbreviation Terms

Term	Definition
➢ RVR	o HCV RNA negative (<50 IU/mL) at week 4
➢ EVR	o Negative or > 2 log decrease in HCV RNA at week 12
➢ SVR	o HCV RNA negative 24 weeks after end of treatment

If EVR (65% of patients with HCV genotype 1) is achieved on therapy, the viral load should be rechecked at 24 weeks. If it remains detectable, treatment should be terminated at that point (Figure 6), whereas if the HCV viral load is negative, treatment should continue for 48 weeks. If EVR is not achieved, treatment may be stopped at 12 weeks, because the chance of a SVR is now remote. It is not necessary to test for EVR in Genotype 2 and 3 patients, because of the high rate of treatment success. The monitoring of these patients on treatment is therefore much simplified. Predictors of a sustained virological response are listed in Table 15.

Table 15. Predictors of sustained response to interferon treatment in HCV infection

- o Genotype 2 or 3
- o HCV RNA < 800,000 IU/mL
- o RVR
- o Age < 40
- o Short duration of infection
- o Absence of bridging fibrosis/cirrhosis
- o Female
- o Ethnicity other than African-American
- o <33% steatosis on histology
- o Absence of diabetes mellitus
- o Certain IL28B polymorphisms
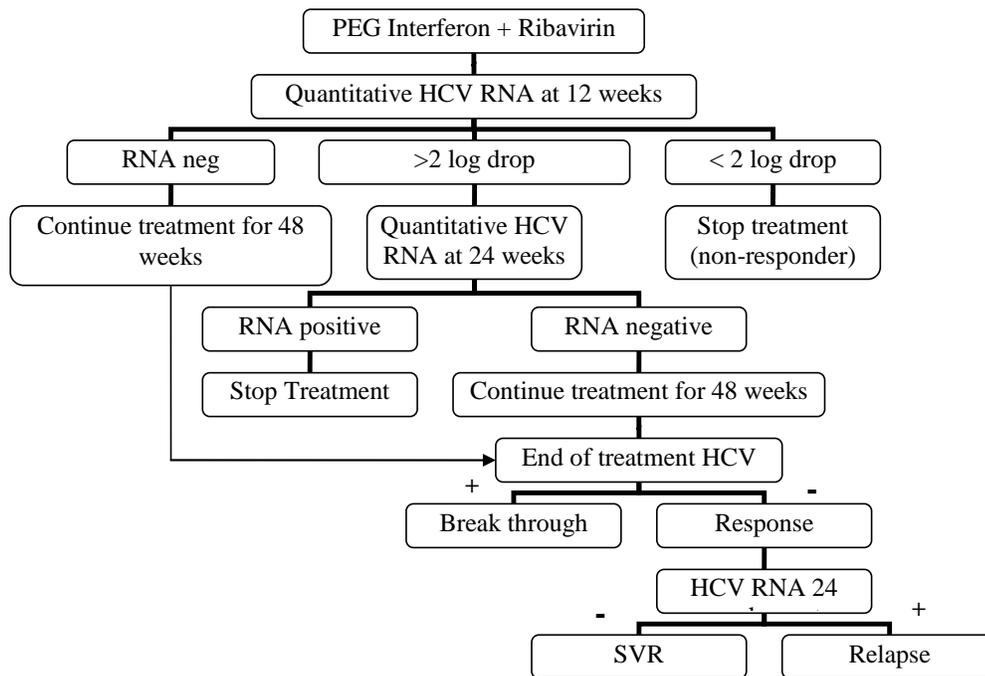
Figure 6. Monitoring treatment response in genotype 1 HCV patients on PEG-.

Treatment of chronic hepatitis C should be considered in all patients without contraindications. The decision to initiate treatment is complex and needs to be individualized on the basis of virologic features as well as patient factors that influence the risk for disease progression and likelihood of treatment response. Patient motivation is essential for treatment adherence. In general, hepatic inflammation (elevated transaminases and active inflammation on liver biopsy), degree of hepatic

fibrosis as well as virologic evidence of infection (positive HCV RNA), are considerations in the decision to start treatment initiation. Patients with normal liver enzymes, cytopenias, cirrhosis and HIV-HCV co-infection may also be considered for treatment by experienced practitioners.

Since a liver biopsy is the most sensitive way to determine the level of hepatic inflammation and fibrosis, it is recommended but not mandatory prior to initiating therapy (Canadian Consensus guidelines, 2007). Patients with genotype 2 and 3 infection may not need liver biopsy because of their high likelihood of cure with treatment.

The therapeutic agents available to treat chronic hepatitis C have evolved in the last 15 years. Current therapy is a combination of pegylated interferon and ribavirin, an oral nucleoside analog. There are two pegylated -IFN preparations available in Canada (PEGASYS (α -2a) and PEGINTRON (α -2b)). The IDEAL trial found that both had similar efficacy, ie. similar SVR rates.

The combination of PEG-IFN and ribavirin has achieved SVR of 42-60% in genotype 1 patients, and 70-90% in genotype 2 and 3 patients. Genotype 1 patients are generally treated for 48 weeks, and genotype 2 and 3 for 24 weeks. Contraindications to treatment are included in Table 16, and adverse effects and monitoring of therapy in Table 17. New HCV-specific protease inhibitors such as telaprevir and bocepravir, used in combination with current standard of care will elevate SVR in genotype 1 to the 65-70% range.

Table 16. Contraindications to IFN and ribavirin therapy

o Pregnancy	o Solid Organ Transplantation (other than liver)
o Alcohol or other substance abuse	o Uncontrolled Depression/Psychosis
o Hepatic Decompensation	o Autoimmune Disease
o Ischemic Heart Disease	o Chronic renal failure

Adapted from the Canadian Consensus Guidelines, 2007

Table 17. Adverse effects and monitoring requirements with IFN and Ribavirin

PEG IFN α (2a,2b)		Ribavirin	
o Flu-like symptoms (headache, nausea, fatigue, fever)	-CBC week 1,2,3,4,6,8,10,then q monthly	o Hemolytic anemia	-CBC as per IFN
o Thrombocytopenia, Leukopenia	-TSH q 3 monthly	o Rash	-Pregnancy tests regularly
o Weight Loss	-Weight q 3 monthly	o Weight loss	
o Depression, Anxiety, Insomnia	-ALT, bili, glucose, U/A q monthly	o Anorexia, nausea	
o Worsening of autoimmune diseases (thyroid, psoriasis, autoimmune hepatitis)		o Cough, dyspnea	
o Reversible alopecia		o Teratogenicity	
o Retinopathy			

No vaccine for HCV yet exists. Newer nucleoside analogues, such as bocepravir or telapravir used in conjunction with PEG-IFN and Ribavirin are still in clinical trial but promise significantly higher rates of SVR, even in genotype 1 infection.

Condoms should be used during the acute phase of HCV illness and indefinitely for those who are immunocompromised. After being advised of the risks of HCV, couples in whom one is chronically infected with hepatitis C must make their own decision with regards to condom use. The risk of spread to regular sexual partners is estimated at 2-5%. In clinical practice, most couples choose not to use condoms, as the risk of spread may only be increased in acts of intercourse where there is exposure to blood of the infected partner.

Vertical transmission of HCV from a mother to newborn is rare, but, the risk of HCV vertical transmission is much higher if the infected mother is also co-infected with HIV (15%). Breast feeding by HCV-infected mothers is considered to be safe.

5. Hepatitis D Virus (HDV)

Chronic hepatitis D usually results from HDV super-infection of an HBV carrier. Less commonly, acute HBV/HDV co-infection leads to chronic infection. Either way, chronic hepatitis D is usually aggressive and severe with rapid progression to cirrhosis. HDV is rare in North America.

The diagnosis is made by testing for anti-HDV in the serum of HBV carriers who have risk factors for HDV infection. HDV antigen and HDV-RNA in serum or liver can also be measured, but only in a limited number of laboratories. In North America this virus is most often transmitted by intravenous drug abuse, and possibly also through the sexual route. In Mediterranean countries intra-familial transmission has been reported. Treatment with interferon for HDV infection has been disappointing. Similarly, the use of lamivudine either alone or in combination with interferon has also been ineffective. Because of the dependency of HDV on HBV, the prevention of HBV infection with vaccination can prevent HDV infection.
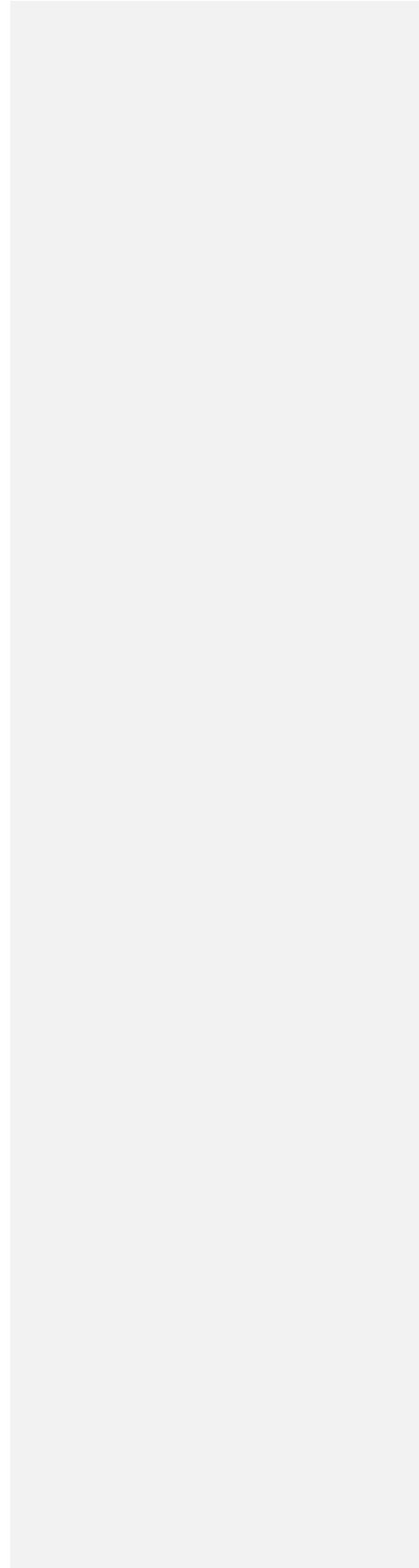
Chapter 17: Fatty Liver Disease
N. Hilzenrat, E. Lamoureux and A. Szilagyi

1. Introduction

The association between development of liver disease progressing to cirrhosis and obesity in low-alcohol-consuming individuals was described a few decades ago. However, only in the last 10 years the importance and the scale of the problem have been realized, likely due to the alarming epidemic of obesity that is currently sweeping the globe.

NAFLD (non-alcoholic fatty liver disease), represents a spectrum of disease. The earliest recognizable stage is steatosis or nonalcoholic fatty liver (NAFL) which represents fat accumulation in liver tissue without inflammation. However, non-alcoholic steatohepatitis (NASH), the next stage, is characterized by steatosis and liver inflammation either with or without fibrosis. The former stage is probably benign opposed to the later stage which has higher risk of progression to cirrhosis and its complications, portal hypertension and hepatocellular carcinoma. Currently only histological examination is able to differentiate between the two stages.

NAFLD is also classified into primary and secondary types (Lazo 2008). The primary type is commonly found among people with conditions of insulin resistance state such as obesity, type 2 diabetes (T2DM) and metabolic syndrome. The secondary type can be associated with the use of certain medications and a variety of miscellaneous disorders that include infectious, nutritional, surgical and inborn errors of metabolism (Diehl 2005, Preiss 2008). Table 1 outlines conditions and factors associated with secondary causes of fatty liver. This chapter will focus on primary NAFLD.

Table 1: Common etiologies of secondary NAFLD - medication, infection, nutrition, surgery and inborn errors of metabolism. Based on references (Diehl 2005, Preiss 2008).

- Amioderone, diltiazem, steroid, tamoxifen, antiretroviral, L-Asparaginase, Bleomycin etc.
- Hepatitis C [HCV]
- Total Parenteral Nutrition [TPN]
  Severe weight loss
- Jejunoileal bypass
- Abetalipoproteinemia, Galactosemia, Glycogen storage disease, Hereditary fructose intolerance, Homocystinuria etc.

2. Epidemiology of NAFLD

One of the major risk factors for the accumulation of excess liver fat is obesity, which leads to insulin resistance. Therefore, the prevalence of NAFLD increases in parallel with the weight or body mass index (BMI) of the groups which were studied. The prevalence of NAFLD in unselected populations from developed countries is estimated between 20 and 30%. It is estimated that 2-3% of the same population will have NASH. In obese individuals (BMI >30 kg/m^2), the prevalence of steatosis is about 65-75% and the prevalence of NASH increases to 15-20%. Several studies have described a higher prevalence of NAFLD among people with T2DM compared with nondiabetics, with prevalence estimates ranging from 40% to 69%. Patients with T2DM appear to have more severe forms of the disease, including NASH and fibrosis (Lazo 2008).

NAFLD has even distribution between men and women. It has been postulated that female hormones may protect against NAFLD. NAFLD can be found in all age groups; however, the prevalence appears to increase with age. Surprisingly, African Americans have significantly less hepatic steatosis than non-Hispanic whites in U.S, even after adjusting for obesity and diabetes(1).

3. Clinical presentation

Most individuals with NAFLD are asymptomatic. The diagnosis is often made following abnormal findings on routine biochemistry or following the detection of an abnormal abdominal ultrasound performed for another reason. Symptoms, when present, may include fatigue and right upper quadrant pain. Hepatomegaly is the most commonly reported finding on physical exam.

If cirrhosis eventually develops prior to the diagnosis of NASH, the presentation is similar to other causes of liver cirrhosis. NAFLD is now recognized as the most common cause of cryptogenic cirrhosis, and has been the underlying diagnosis in about 10% of liver transplant cases (4).

4. Diagnosis

Fatty liver is associated with elevated concentrations of serum ALT and GGT. But neither is sufficiently sensitive nor specific to make the diagnosis of NAFLD. It is important to emphasise that AST can be higher than ALT in cirrhosis. Therefore, in patient with known NAFLD, a rising AST may suggest a bad prognostic sign. ALT and GGT appear to correlate with the amount of liver fat present as measured by abdominal MRI or ultrasound (Diehl 2005, Wieckowska 2008).

A combination of serum adiponectin, Homoeostasis Model Assessment of Insulin Resistance (HOMA-IR) and type IV collagen 7S has a sensitivity of 94% and specificity of 74% for identifying early NASH. In another study, hyaluronic Acid (HA) levels were significantly different between patients with steatosis only and NASH. Moreover, HA levels were the strongest independent predictor of severe fibrosis (Preiss 2008). Predictors for NAFLD are listed in Table 2.

Table 2: Risk factors and predictors for Non-Alcoholic Fatty Liver Disease. Most variables do not distinguish between NAFLD and more advanced disease (Lazo 2008, Preiss 2008, Wieckowska 2008).

➤ Obesity	o Body Mass Index > 28 mg/m^2
➤ Marker of Insulin Resistance	o Calculation of HOMA-IR
➤ Type 2 Diabetes	o Abnormal Hgb A-1c
➤ Sleep Apnea	o may be part of the metabolic syndrome
➤ Hypertension	o may be part of the metabolic syndrome
➤ Dyslipidemia	o Triglycerides especially elevated
➤ Age	o older [but 10% of children affected]
➤ Hypothyroidism	
➤ Elevated ALT	o Mild [< 3N]
➤ Elevated GGT	
➤ AST usually normal	o elevated with excess alcohol or more advanced NASH with cirrhosis.
➤ Abdominal Ultrasound	o Useful with > 30% hepatic fat o Appears echogenic (bright).

Steatosis may be diagnosed by ultrasonography (US), computerized tomographic (CT) scanning or magnetic resonance imaging (MRI). US is currently the preferred method for screening asymptomatic patients with elevated liver enzymes and suspected NAFLD.

US findings of fatty liver include hepatomegaly, diffuse increase in echogenicity of the liver parenchyma (brightness), and vascular blunting. US is the least expensive option to investigate NAFLD, and has been reported to have a sensitivity of 89% and specificity of 93% for the identification of fatty liver. Drawbacks to ultrasound however, include the requirement that at least 30% of the hepatocytes are fat-filled, and in the morbidly obese the performance of ultrasound is considerably weaker (Wieckowska 2008).

Both CT scanning and MRI are sensitive techniques for quantification of steatosis, which is particularly useful in clinical studies. More recently, localized proton magnetic resonance spectroscopy (MRS), has been shown to be a noninvasive method that is highly accurate in measuring hepatic triglyceride content. Unfortunately, currently none of these imaging methods has a role to distinguish between the various stages of NAFLD (Wieckowska 2008).

Transient elastography (Fibroscan®), a non-invasive technique used to measure liver tissue stiffness, provides information on the severity of fibrosis. There is a good correlation between the histological staging of fibrosis and Fibroscan® results. This led to a suggestion that the number of liver biopsies might be reduced. However, significant intraobserver variability has been reported for this device, and therefore at present Fibroscan® is not reliable for the diagnosis of fibrosis in patients with fatty liver (Wieckowska 2008).

Xe‑133 liver scan is a safe, reliable and non-invasive test for the diagnosis and quantification of hepatic steatosis. The Xe-133 scan that is superior to abdominal ultrasound (Ghali P, personal communication, 2011).

The available noninvasive methods are useful to identify the presence NAFLD, but they lack unfortunately, both pecificity and sensitivity to distinguish NAFL from NASH. This represents a key clinical problem, because only patients with NASH progress to cirrhosis. Those NASH patients are those who need close monitoring and follow up, and as well are the potential targets for therapeutic intervention. Thus, a liver biopsy remains the gold standard for the diagnosis of NAFLD.

Histology continues to provide the only proven method to diagnosed NAFLD, to distinguish between NASH and steatosis, and to provide prognostic information. At present, there are no clear practice guidelines for biopsy in NAFLD. Liver biopsy has clinical risk, and has the potential for false negatives. Moreover, there is still lack of consensus regarding histological criteria for classification of NAFLD.

In order to reduce the need for liver biopsy, several algorithms have been developed to detect individuals with a higher likelihood of having fibrosis in NASH. For example, significant fibrosis was found in patients above age 45 years and who have abnormal liver enzymes with no clear explanation, BMI >28 kg/m^2 , hypertriglyceridemia and type 2 diabetes (Preiss 2008). Currently, it is suggested that liver biopsy should be limited to those persons who are more likely to have a high fibrosis stage. These include: age >45 years, AST/ALT ratio >1, Type 2 diabetes, BMI >30 kg/m^2 , those with persistent elevations of serum liver enzymes despite weight loss, and in case of diagnostic doubt (Preiss 2008).

5. Liver histopathology in NAFLD

Since the first designation in 1980 by Ludwig (Ludwig 1980) under the name of NASH (nonalcoholic steatohepatitis) of alcoholic-like changes in the liver of patients with other

conditions such as obesity and diabetes, there has been a rich literature on NAFLD and NASH. Brunt (Brunt 2010) and Lefkowitch (Lefkowitch 2010) have described and illustrated thoroughly the histopathologic changes of steatosis and steatohepatitis related conditions and differential diagnosis.

The liver biopsy interpretation remains the "gold standard" in the diagnostic approach of NAFLD. By using a standardized method of reporting, the pathologist assesses the severity of disease and thereby assists the clinician in the follow-up of disease, documenting the progression of disease towards cirrhosis or its regression. Also, liver biopsy is useful in the recognition and assessment of any coexisting liver disease.

The recognition of NAFLD is done not on one pathognomonic morphologic alteration, but rather on the basis of a combination of lesions, to be interpreted in light of clinical context (Figure 1). The first lesion is the steatosis, mostly macrovacuolar (often mixed), with a large intracytoplasmic lipid vacuole (or intracytoplasmic multiple lipid droplets) pushing the nucleus to the periphery of the hepatocyte, with a centrilobular accentuation of involvement. The severity of steatosis is assessed by an estimate of the percentage of fatty hepatocytes (or acini) (Chalasani 2008): less than 33%, between 33 and 66%, and over 66%. The minimal amount of steatosis required for a diagnosis of NAFLD is more than 5% .
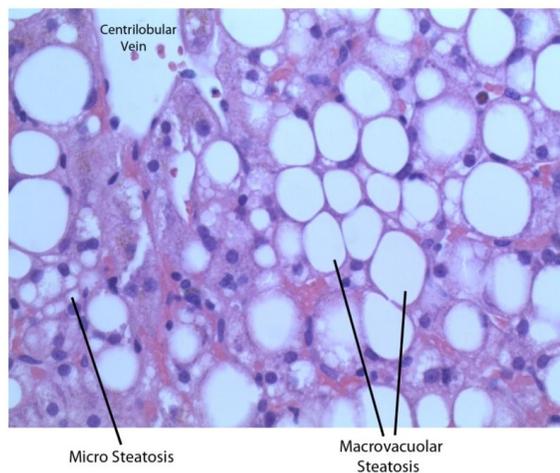
Figure 1. Steatosis (H&E, x40)

A diagnosis of NASH is made when there are signs of liver cell damage (hydropic and ballooning changes of hepatocytes, Mallory's bodies, apoptotis) associated with a variable, but usually mixed inflammation (polymorphonuclear neutrophils and mononuclear cells) (Figure 2). A mild degree of mononuclear portal inflammation may be present. With persistence or progression of disease, these necroinflammatory lesions are likely to lead to a pericellular fibrosis at sites of damage, i.e. with a centrilobular accentuation. Later, a portal and periportal fibrosis appears. Then, the lobular and portal fibrosis becomes confluent and eventually results in cirrhosis. The presence of fibrosis is not necessary for a diagnosis of NASH. Steatosis, ballooning hepatocytes, Mallory's bodies, inflammation both lobular and portal, and fibrosis are the most significant findings; however, other lesions have been documented in NAFLD and NASH, such as glycogenated nuclei, megamitochodria.
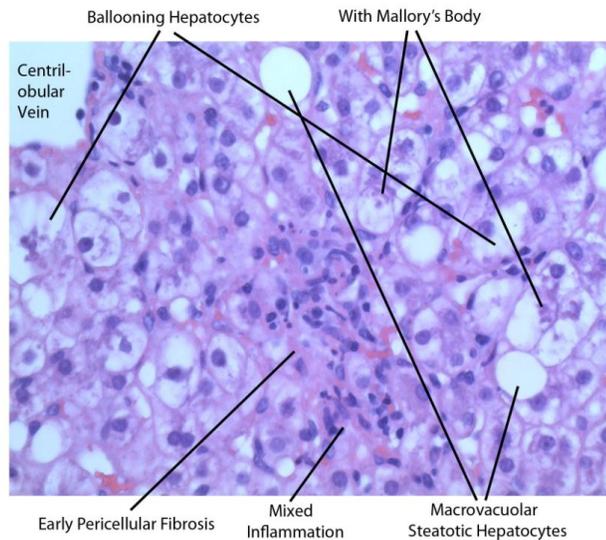
Figure 2. Steatohepatitis (H&E, x40)

In reporting the assessment of steatosis, the presence and severity of the necroinflammatory lesions, and the extent of fibrosis, we use the semiquantitative method of grading the "activity" (3 grades) and staging the fibrosis (4 stages), developed by Brunt and *colleagues*, in 1999 (Brunt 1999) (Table 3). In grading the activity or necroinflammatory lesions, the severity of steatosis has little influence; rather, the grading is influenced by the amount of ballooning, and both lobular and portal inflammation.

Table 3. Grading activity and staging fibrosis in NASH (reproduced & adapted from Brunt 2010).

➤ **Grading Activity**

Grade	Steatosis	Ballooning (distribution-severity)	Inflammation/20X field Lobular	Portal
	1: <33%		L0: absent	P0: absent
	2: 33-66%		L1: <2foci	P1: mild
	3: 66% and +		L2: 2-4 foci	P2: mod
			L3: >4 foci	P3: severe.
G-1 (mild)	1-2	minimal- zone 3	L 1-2	P 0-1
G-2 (moderate)	2-3	present- zone	L 1-2	P 1-2
G-3 (severe)	2-3	marked- mostly zone	L 3	P 1-2

➢ **Staging Fibrosis**

STAGE Fibrosis	Zone 3 perisinusoidal focal or extensive	Periportal fibrosis focal or extensive	Bridging fibrosis	Cirrhosis probable or definite
1	X	-	-	-
2	X	X	-	-
3	X	X	X	-
4	X	X	X	X

The diagnosis has some limitations. NAFLD and NASH have various etiologic associations and the pathologist can rarely be specific about these. The main differential diagnosis is a steatohepatitis due to alcohol, which has similar histopathological features. It is more difficult to make the diagnosis particularly during the end stage of the disease, when some morphologic elements may be missing (such as lacking of steatosis).

In the pediatric population, NAFLD and NASH differ from those found in the adult. These differences include a portal inflammation and fibrosis rather than a centrilobular pericellular fibrosis as the first manifestations of fibrosis (Schwimmer 2005). These differences brought the NIH-sponsored NASH Clinical Research Network (Brunt 1990*) to suggest a modified scheme of staging of fibrosis. They propose a subclassification of stage 1 in 3 subcategories to reflect this difference in the distribution of the first manifestation of fibrosis between the adult and pediatric disease.

6. Pathogenesis of NAFLD

The pathogenesis of NAFLD is not completely clear. The two major risk factors to develop NAFLD are obesity and insulin resistance. Development of NAFL, progression to NASH, cirrhosis and in some cases hepatocellular carcinoma can take 20-40 years. The advanced part of this process may be genetic, with the early part initiated by environmental factors. The two-hit hypothesis is now the widely accepted theory of the pathogenesis of NAFLD and its progression. The concept is based on the observation that only some 10% of patients with NAFLD progress to NASH, and only some 15% of these will develop cirrhosis (Lazo 2008, Preiss 2008, Jou 2008).

How obesity leads to insulin resistance and later to NAFL is the first basic question. Insulin resistance is a result of an abnormal metabolic mutual relationship between the adipose tissue, and the skeletal muscles which utilize most of the plasma glucose. In the normal subject, following a meal, the skeletal muscle cell utilizes glucose which is inserted into the cell following insulin attachment to its receptor. The receptor activates a cascade of proteins by a series of phosphorylation reactions, which stimulate the translocation of the glucose transporter 4 (Glut4) from intracellular vesicles to the plasma membrane (Choi 2010). Insulin inhibits lipolysis in adipocytes. However, in the fasting state when the level of insulin is low, lipolysis starts in the adipose tissue. Plasma free fatty acids (FFAs) become the principal fuel source of skeletal muscle. Excess of caloric intake leads to adipocyte hypertrophy, which in turn leads to the secretion of large amounts of adipokines such as monocyte chemoattractant protein-1 (MCP-1). MCP-1 enhances macrophage infiltration and secretion of TNF-α, IL-1β and others cytokines.

High TNF-α level results in decreased fatty acid esterification and enhanced lipolysis (14). Elevation of plasma FFA concentration in insulin sensitive individuals leads to an increase in the intramyocellular fat content. High concentrations of FFAs lead to malfunction of the insulin signaling pathway (Choi 2010, Guilherme 2008) and significant reduction in both the quality and quantity of the mitochondrial density in skeletal muscle cells. These in turn lead to an insulin resistant state.

Normal FFAs metabolism in the liver depends upon balances of hepatocyte uptake and *de novo* synthesis of FFAs on one hand, and disposal of FFAs by *de novo* triglyceride synthesis of the other, which then leads to export of FFA's as VLDL, and their oxidation.Thus, obesity is a chronic inflammatory state which causes lipolysis in the adipose tissue, as well as significant increases in circulating nonesterified FFAs. A high insulin level activates transcription factors, such as sterol responsive element binding protein-1c (SREBP-1c) and carbohydrate response element binding protein (ChREBP). These transcription factors increase *de novo* lipogenesis, and lead to the accumulation of triglycerides into histologically visible macrovesicles in the liver (Cheung 2008)). In the hepatocytes, FFA oxidation occurs in subcellular organelles.

Further, a high‑fat diet may produce changes in the intestinal microflora, increase plasma LPS levels, and lead to the development of a "metabolic endotoxemia," which progresses to NAFLD, at least in animal models (Serino 2009).

7. Treatment of Fatty Liver
7.1. Calorie Restriction

Therapy of fatty liver begins with recognition of the condition. The epidemic of obesity besides the increasing prevalence of fatty liver is also driving an increased incidence of the metabolic syndrome, type 2 diabetes, and consequent cardiovascular effects. It is expected and hoped that the best treatments for NAFLD and NASH would also treat other aspects related to fatty liver. In this respect global treatment with regular [not fads] diet, exercise and lifestyle would fit this requirement the best. Within this paradigm the role of bariatric surgery, the most extreme form of forced weight loss supports the notion of ideal therapy.

Musso and co-workers summarized randomized controlled trials of various treatment modalities in fatty liver (diet, lifestyle, specific dietary components and pharmaceutical interventions) (Musso 2010). A total of 10 trials addressing either NAFLD or NASH were reviewed, dealing with weight reduction without or with lifestyle changes (including exercise) or addition of dietary aids. These dietary aids included a carbohydrate or lipid absorption inhibitor or antioxidant vitamins. In studies reporting diabetics their proportion included ranged from 10‑100%. The mean duration of studies was 7.9 months, with a range 1‑24 months.

Three studies which evaluated weight reduction alone suggested that a minimum of 7% loss is needed to result in some improvement in NASH, including loss of fat and NASH activity score. Intense life style changes over one year also resulted in improvement in two trials. Importantly the institution of physical exercise alone independently improved NAFLD parameters in three trials. A study that was not included in the systematic review supported an interesting observation that cardiovascular fitness, (independent of MRI assessment of adiposity) was related to liver fat (Kantartzis 2009).

The last area of diet reported was the role of specific dietary components especially carbohydrates. Evaluation of carbohydrate restricted diet in obese diabetics resulted in improved insulin sensitivity although again the effect of minimum 8% weight loss was evident in improving hepatic fat (Musso 2010).

The proof of principle that calorie restriction improves metabolic syndrome and its complications, including NAFLD and NASH, is provided by bariatric surgery. In a meta-analysis of 15 studies on this type of surgery, Mummadi found that of over 750 patients with paired liver biopsies had substantial improvements (Mummadi 2008). Body mass index was reduced from 19-42% by a variety of types of bariatric surgery. These operations included Roux-en-Y gastric bypass [8 studies], laparoscopic adjustable gastric band [Lazo 2008], gastroplasty [Diehl 2005], biliopancreatic diversion [Lazo 2008], vertical band gastroplasty [Lazo 2008], sleeve gastrectomy and bilio-intestinal bypass in combinations [Diehl 2005]. Repeat liver biopsies were performed between 2-111 months. The results were impressive, with 69.5% (95% CI 42.4 - 90.8 %) of patients showing complete resolution of NASH. Individual histologic features evaluated before and after surgery revealed 91.6% (95% CI, 82.4- 97.6 %) improvement or resolution of steatosis, 81.3 % (95% CI, 61.9 - 94.9 %) improvement in inflammation, and 65.5 % (95% CI, 38.2- 88.1 %) in fibrosis (20). Surgical intervention to alter anatomy should be the last resort, after life-style changes have been extensively and sincerely tried and failed.

The conclusion to be drawn from analyses of these studies is that even mild (7%) weight loss improves fatty liver. Rather than "fad" diets, total caloric restriction should be the goal of dietary therapy in persons with NAFLD. In addition, the restriction of total fat and carbohydrates may be beneficial. Because saturated fatty acids increase oxidative stress, these should likely also be curtailed. In addition, simple sugars and high fructose containing foods should be specifically avoided since these are thought to aggravate obesity. Finally, alcohol consumption should be restricted in individuals with risk factors (Vuppalanchi 2009). In general, rapid weight loss of more than 2 pounds (1 kg) per week is not recommended, because there is a small risk of rapid weight loss aggravating liver function. Secondly, physical activity even independently from diet may improve the liver through improved insulin sensitivity. The recommended time of physical activity is about 30 to 45 minutes a day. This could include a brisk walk or aerobic exercises.

Unfortunately, our current environment with an abundance of calories and the economic push to consume more is difficult to overcome.

7.2 Pharmaceutical Agents

When lifestyle modification and diet fails the longterm prognosis of NASH in particular is associated with an increased liver related mortality (Rafiq 2009). Furthermore, not all these patients are willing or represent good surgical candidates. Nevertheless it is important to reduce NASH and its complications. Unfortunately, at this time, no drug is approved for use.

There have been numerous specific dietary or pharmacological agents with or without addition of dietary components [mainly vitamin E or C] which have been tried to improve either fatty liver or the more advanced NASH. Therapies are generally aimed at reversing insulin resistance with the hope that this also reverses fatty acid accumulation and its consequences. Therapy is also aimed at preventing or reversing the hypothesized second hit phenomenon of increased oxidative stress. Most information is based on randomized controlled studies (RCT).

An interesting publication by Loomba et al. evaluated the expected outcome of placebo in randomized control trials (RCTs) in NAFLD/ NASH. In a meta-analysis of 5 trials encompassing some 162 patients, the authors concluded that improvement in ALT is to be expected, but does not accurately reflect hepatic events. However, only a 1 point improvement is expected overall in histologic NASH scores (Loomba 2008). Not all studies evaluate results from these perspectives.

Table 4 lists agents used in clinical trials or only in animal models, with the rationale of their use. Because insulin resistance is a major pathogenic component of fatty liver, drugs used in treatment of diabetes have been used extensively in this condition. Recall, however, that the relationship between insulin resistance and liver histology is poor (Ratziu 2010). Other agents affect lipid transport, while still others have been used to concentrate on reducing oxidative damage and mitochondrial injury. Also, because the second hit is accompanied by inflammatory cytokines , inhibitors of tumor necrosis alfa have been studied, with varying success. Several "natural " products also have been tried. These include both herbal products and the currently popular probiotics [exogenous bacteria which bypass digestion and confer health benefits to the host]. These bacteria affect many gut functions and improve gut barrier permeability, which could decrease bacterial translocations limiting hepatic second hit injury.

Table 4. Outline of therapeutic agents and their proposed mechanism of action for non-alcoholic steatohepatits (NASH).

Agent	Mechanism[s]
➢Metformin	○Stimulates aerobic metabolism, reduces FFA oxidation, decreases uncoupling protein, increases IS
➢Thiazolidinediones (Glitazones)	○Stimulates PPaR-γ, Adipokine, improves IS, increased FFA oxidation
➢TNF – α inhibitors (Pentoxifyline)	○Reversal of lipid induced increase in proinflammatory cytokines
➢Ursodeoxycholic Acid	○Improves nuclear cell signaling ○Increases GLP-1 and brown fat energy expenditure
➢Statins	○Increases β – oxidation, adiponektin ○With IS, reduces AGE [which promotes NASH]
➢Fibrates	○Agonist of PPar – γ, increases high ○Density cholesterol
➢Probucol	○Antioxidant and antiinflammatory ○Effects
➢Endocannabinoid receptor antagonist (rimonanbant)	○Reduces fat mass, insulin levels and liver triglycerides; increases adiponectin
➢Angiotensin II type 1 Converting Enzyme receptor (Telmisartan)	○Imporves IS via PPaR – γ partial agonist effect
➢Carnitine	○Facilitates long chain FFA transport ○Across mitochondrial membrane
➢Betaine	○Reduces lipid accumulation in liver by ○Donating methyl groups to homo-cysteine
➢Vitamin E and C	○Inhibits FFA deposition by reducing ○Oxidative stress

Agent	Mechanism[s]
➢Polyunsaturated fats	○Improves serum triglycerides and IS
➢Yo Jyo Hen Shi Ko	○Antifibrotic and hepatocelluar protection
➢Green tea	○Antioxidative effects, and lowers serum lipids
➢Probiotics	○Improves bowel permeabilty and reduces bacterial translocations

Abbreviations: Advanced glycation endproducts, AGE; Free Fatty Acids, FFA; Glucagon-like peptide 1, GLP-1; Insulin sensitivity, IS;, Peroxisome proliferator – activated receptor gamma, PpaR – γ; and Tumor necrosis alpha, TNFα.

Trial outcome of drugs or specific dietary agents have been variable and follow-up has been relatively short. At least three, largely overlapping meta-analyses of RCTs were published in persons with NAFLD. The first by Socha included 15 combined therapeutic studies (Socha 2009). This study showed that metformin but not pioglitazones improved serum biochemistry, as compared with vitamin E. A second meta-analysis by Rakoski et al. evaluated only those studies using either the glitazones [5 studies] or metformin [4 studies] (Rakoski 2010). In contrast, they reported that glitazones but not metformin statistically improved ALT, as well as histologically determine steatosis and ballooning of hepatocytes. Even in the NAFLD groups without diabetes, the glitazones improved inflammation and fibrosis. The most comprehensive meta-analysis by Musso et al reviewed 49 RCTs, 23 [22 NASH and 1 NAFLD study] of which included pre- and post-liver biopsies (Musso 2010). Table 5 outlines the agents, the numbers of studies analyzed, and the odds ratios with significance for outcome of trials with comparisons of pre- and post-treatment liver biopsies. Their conclusion about insulin sensitizers was that glitazones improved histological steatosis and inflammation, but increased the patient's body weight. Antioxidants had variable outcome. In 1 RCT, each pentoxifyline [TNFα inhibitor], telmisartan [Antihypertensive], and L-carnitine [facilitates lipid transport] improved liver histology.

Table 5A. Outline of studies included in meta-analyses of various agents for treatment for non-alcoholic steatohepatitis (NASH), according to histological outcome.

Agent	Number of studies	Steatosis	Inflammation	Fibrosis
Thiazolidinediones	5	4.06, p<0.00001	3.53 P<0.00001	1.4 P=0.17
Metformin	4	1.3 NS	1.08 NS	0.9 NS
Satatin (simvastatin)	1	0.56 NS	0.00 NS	0.17 NS
Ursodeoxycholic Acid	2	1.15 NS	0.78 NS	0.94 NS
Antioxidants	5	1.26 NS	1.19 NS	0.64 P=0.07
Pentoxifyline	1	1.78 NS	12 P=0.04	1/07 NS

Telmisartan	1	1.56 NS	4.13 P=0.03	3.85 P=0.02
L-Carnitine	1	23.5 P=0.03	7.2 NS	2.21 NS

NS, Not Statistically Significant
Study times ranged from 1-24 months. Agents, the number of studies included in analysis summary odds ration and statistical significance is listed. In the majority of studies a Fixed model was used. Antioxidants and metformin fit a Random model better in fat and inflammation, These results are derived from reference (Musso 2010).

Based on these analyses, the glitazones hold the best promise at this time, with Pioglitazone being the most successful. Adverse side effects are low, although body weight gain, mild congestive heart failure, and osteopenia with fractures have been described (Ratziu 2010). Studies with antioxidants, especially vitamin E, may also have some use. Single studies showing individual positive effects need to be verified. Overall changes in lifestyle should be implemented first, or also in conjunction with any pharmaceutical therapy. In properly selected candidates especially, those with BMI > 35 kg/M^2, bariatric surgery is a good alternative.

Table 5B. Proportion of patients (%) [with pre and post liver biopsies] improving after bariatric surgery for NASH in 3 histologic categories is shown together with 95% confidence intervals. Results based on reference (Choi 2010)

Agent	Number of studies	Steatosis	Inflammation	Fibrosis
Bariatric surgery	15	91.6%	81.3%	65.5%
		(82.4, 97.6)	(61.9, 94.9)	(42.4, 94.9)

8. Summary

NAFLD is a problem paralleling the epidemic of obesity, and could be potentially controlled by efforts which reduce weight and alter sedentary lifestyles. While there is no proven or approved pharmaceutical treatment of NASH several agents especially the "glitazones" hold promise. Several other agents with good outcomes need further verification. Surgery is a last resort for those in whom other efforts fail. With a sizeable proportion of NAFLD patients developing NASH, and some of these likely to progress to cirrhosis with all of its many complication, it is clear that the obesity epidemic may progress to another epidemic, chronic liver disease. Sucessful means are urgently needed to reduce this possibility.

Chapter 18: Alcoholic Liver Disease
F. Wong

1. Epidemiology

Liver disease is the fourth commonest cause of death in adults between the ages of 20 to 70 years in Canada. Alcohol is still one of the commoner causes of chronic liver disease in this country. Not all those who abuse alcohol develop liver damage. The incidence of cirrhosis amongst alcoholics is approximately 10 to 20%. The mechanism for the predisposition of certain people to develop cirrhosis is still unknown. The amount of alcohol ingested has been shown in epidemiological studies to be the most important factor in determining the development of cirrhosis. Males drinking in excess of 60 gm and females in excess of 40 gm of alcohol per day for 10 years are at a high risk of developing cirrhosis. The alcohol content rather than the type of beverage is important and binge drinking is less injurious to the liver than continued daily drinking. Women are more susceptible to liver damage than men. They are likely to develop cirrhosis at an earlier age, present at a later stage and have more severe liver disease with more complications. Genetics may play a role in the development of alcoholic liver disease. Patterns of alcohol drinking behaviour are inherited. Social factors such as the availability of alcohol and social acceptance of alcohol use can also encourage the liberal use of alcohol, thereby increasing the risk for the development of alcoholic liver disease in susceptible individuals

2. Alcohol Metabolism

Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase in the hepatocyte cytosol, and then to acetate by acetaldehyde dehydrogenase in the mitochondria. Cytochrome P-450 2E1 enzymes also convert alcohol to acetaldehyde. Genetic pleomorphism of these enzyme systems can lead to different rates of alcohol elimination, and contributes to the individual's susceptibility to alcohol damage. Some studies have reported an increased frequency of the gene that encodes for alcohol dehydrogenase in patients with alcoholic liver disease, leading to increased production of acetaldehyde. Alcoholics with decreased acetaldehyde dehydrogenase activity also develop alcoholic liver disease at a lower cumulative intake of alcohol than others. Alcohol has a direct hepatotoxic effect and does not require pre-existing malnutrition, but malnutrition may play a permissive role in producing alcohol hepatotoxicity. There is a threshold of alcohol toxicity beyond which no dietary supplements can offer protection. Obesity may also be an independent risk factor for the development of alcoholic liver disease. Finally, viral hepatitis, whether hepatitis B or hepatitis C infection, appears to play a role in the development of advanced alcoholic liver disease. Patients with alcoholic liver disease and viral hepatitis infection tend to develop their disease at a younger age, have more severe histological features and decreased survival. In addition, the presence of viral hepatitis is a major risk factor for the development of hepatocellular carcinoma in patients with alcoholic cirrhosis.

The spectrum of liver disease covers the relatively benign steatosis to the potentially fatal alcoholic hepatitis and cirrhosis (Figure 1).

Excess alcohol

↓

Fatty liver ⟶ resolves with abstinence

Heavy alcoholic binge without eating

(>60 gm in men and >40 gm in women for >10 years)

Alcoholic hepatitis   Alcoholic cirrhosis

⟶

↓

Complications of portal hypertension, and Hepatoma
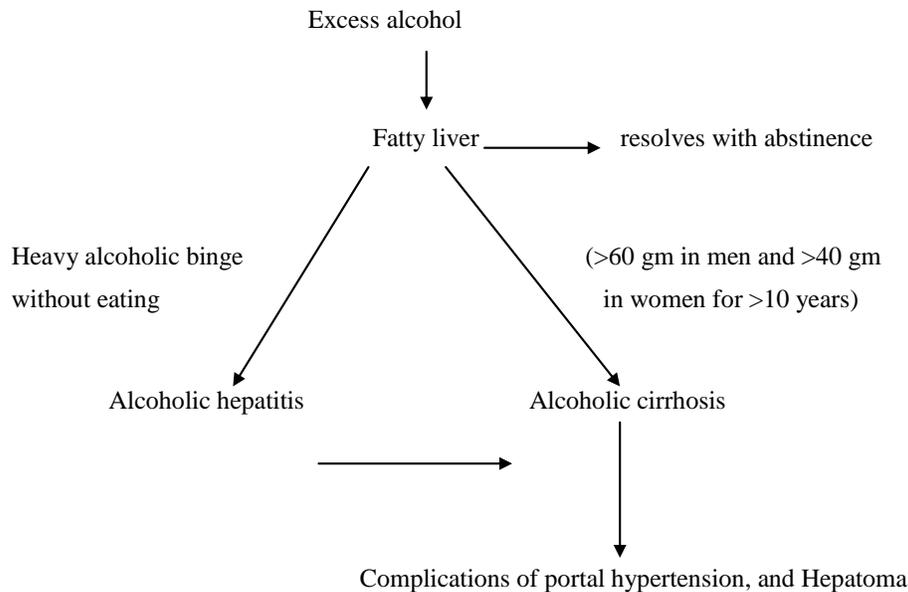
Figure 1. Schematic representation of the progression of the different stages of alcoholic liver disease

3. Alcoholic Fatty Liver

This is the most frequent hepatic abnormality found in alcoholics. It is a toxic manifestation of alcohol ingestion, appearing within three to seven days of excess alcohol intake. Alcohol dehydrogenase and acetaldehyde dehydrogenase cause the reduction of nicotinamide adenine dinucleotide (NAD) to NADH (reduced form of NAD). Metabolic changes associated with ethanol ingestion leads to altered ratio of NAD/NADH, which promotes increased triglyceride synthesis through the inhibition of gluconeogenesis and fatty acid oxidation. There is also impaired lipid secretion by the liver. This results in the accumulation of triglyceride in the hepatocytes, mainly in the terminal hepatic venular zone. In more severe cases, the fatty change may be diffuse. The fat may be macrovesicular (large droplets) or microvesicular (small droplets), which represents more active lipid synthesis by the hepatocytes. Fatty liver may occur alone or be part of the picture of alcoholic hepatitis or cirrhosis.

Clinically, the patient is usually asymptomatic and examination reveals firm smooth hepatomegaly. Occasionally the fatty liver may be so severe that the patient is anorexic, nauseated and has right upper quadrant pain or discomfort. Fatty liver is not specific to alcohol ingestion. The differential diagnoses include obesity, insulin resistance, hyperlipidemia, malnutrition, and various medications. Attribution of fatty liver to alcohol use therefore requires a detailed and accurate patient history. In the case that the fatty liver is related to excess alcohol intake, this usually follows a prolonged heavy alcoholic binge. Liver function tests are frequently normal, although the γGT is invariably elevated whilst the aminotransferases and alkaline phosphatase may be slightly increased. The patient is never jaundiced and hepatic synthetic function (albumin and International Normalized Ratio or INR) is preserved. In the absence of a super-imposed hepatic process, stigmata of chronic liver disease such as spider angiomas,

ascites, or asterixis should be absent. A fatty liver is usually detected by ultrasound. Liver biopsy is required to make a definitive diagnosis and to exclude the presence of steatohepatitis. When fatty liver is not associated with alcoholic hepatitis, the prognosis is excellent. Complete abstinence from alcohol and a nutritious diet will lead to disappearance of the fat over four to six weeks.

4. Alcoholic Hepatitis

Alcoholic hepatitis may occur separately or in combination with cirrhosis. There are all grades of severity. It is a condition characterized by liver cell necrosis and inflammatory reaction. Pathophysiologically, chronic alcohol exposure activates hepatic macrophages, which then produce tumor necrosis factor-α (TNF-α). TNF-α induces mitochondria to increase the production of reactive oxygen species. This oxidative stress promotes hepatocyte necrosis and apoptosis, which is exaggerated in the alcoholic individual who is deficient in antioxidants such as glutathione and vitamin E. Free radicals then initiate lipid peroxidation, which causes inflammation and fibrosis. Inflammation is also incited by acetaldehyde that, when bound covalently to cellular proteins, forms adducts that are antigenic. Alcohol is known to cause an exaggerated gradient of hypoxia from the portal vein to the central vein, suggesting that the hypoxia induced by chronic alcohol use may also contribute to hepatic damage.

Histologically, hepatocytes are swollen due to an increase in intracellular water secondary to increase in cytosolic proteins (Table 1). Steatosis, often of the macrovesicular type, is present. Alcoholic hyaline or Mallory bodies are purplish red intra-cytoplasmic inclusions consisting of clumped organelles, intermediate microfilaments (Figure 2). Polymorphs are seen surrounding Mallory containing cells and also within damaged hepatocytes. Neither fatty infiltration nor Mallory bodies are specific for alcoholic hepatitis nor are they necessary for diagnosis. Collagen deposition is usually present. It is maximal in zone 3 and extends in a perisinusoidal pattern to enclose hepatocytes, giving it a "chicken wiring" effect. Changes in the portal triad are inconspicuous. Marked portal inflammation suggests an associated viral hepatitis such as hepatitis C, whereas fibrosis suggests complicating chronic hepatitis (Table 2). When the acute inflammation settles, a varying degree of fibrosis is seen which may eventually lead to cirrhosis.

Table 1. Histopathological changes of Alcoholic Hepatitis

- Perisinusoidal—maximal changes
  - Hepatocytes—swollen (diffuse, pericentral changes)
  - Intrahepatocyte inclusions—Mallory bodies
  - Fat—macrovesicular steotosis (zone 3)
  - Perihepatocye—polymorphs
  - Collagen (zone 3)—perisinusoidal pattern to enclose hepatocytes ("chicken wiring" affect)

- Portal—minimal changes
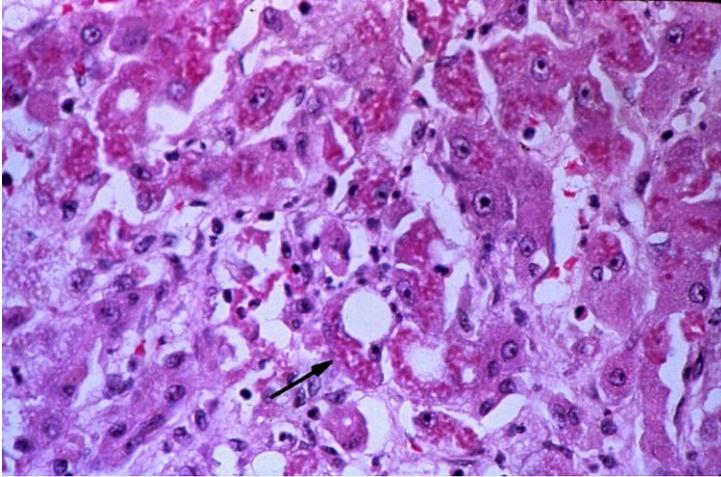
Figure 2. Photomicrograph showing Mallory bodies (arrow) and inflammatory cells, especially polymorphs, in a patient with acute alcoholic hepatitis.

Clinically, mild cases of alcoholic hepatitis are only recognized on liver biopsy in patients who present with a history of alcohol abuse and abnormal liver function tests. In the moderately severe case, the patient is usually malnourished and presents with a two to three week prodrome of fatigue, abdominal pain, anorexia, nausea and weight loss. Clinical signs include a fever of $<40^0$C, jaundice and tender hepatomegaly. In the most severe case, which usually follows a period of heavy drinking without eating, the patient is gravely ill with fever, marked jaundice, ascites, evidence of a hyperdynamic circulation, such as systemic hypotension, and tachycardia. Florid palmer erythema and spider nevi are present with or without gynecomastia. Hepatic decompensation can be precipitated by vomiting, diarrhea or intercurrent infection leading to encephalopathy. Hypoglycemia occurs often and can precipitate coma. Gastrointestinal bleeding is common, due to the combination of a bleeding tendency and portal hypertension. Signs of malnutrition and vitamin deficiencies are frequently present. When alcoholic hepatitis is severe, the differential diagnoses include autoimmune hepatitis, acute viral hepatitis, acute Budd-Chiari syndrome, acute manifestation of Wilson's disease in a younger individual, severe drug-induced liver injury, or a combination of alcohol and acetaminophen. Acetaminophen is a hepatotoxin when taken in large quantity. Alcohol increases the patient's susceptibility to liver damage by acetaminophen due to induction of the metabolizing enzymes and smaller doses of acetaminophen in an alcoholic may precipitate liver failure.

Laboratory abnormalities include elevations of aminotransferases, bilirubin, alkaline phosphatase and γGT (Table 2). The aminotransferase levels rarely exceed 300U/L, except in association with acetaminophen ingestion, with the AST/ALT ratio >2. Hyperbilirubinemia can be quite marked, with levels reaching 300 to 500μmol/L, and is a reflection of the severity of the illness. The increase in γGT is proportionally greater than that of alkaline phosphatase. There is also mild anemia, leukocytosis of up to 20 to $25X10^9$/L, and prolongation of the INR, which does not respond to vitamin K. The serum albumin falls. Serum lgA is markedly increased with lgG and lgM raised to a lesser extent.

Table 2. Laboratory abnormalities commonly seen in persons with alcoholic hepatitis.

➢ Hematology
  o Macrocytic anemia (increased MCV)
  o ↑ WBC
  o ↓ platelets

➢ General chemistry
  o ↑ blood sugar
  o ↑ uric acid
  o ↑ triglycerides
  o Ketosis

➢ Tests of liver function and injury
  o ↓albumin
  o ↑↑bilirubin
  o ↑ INR
  o ↑ AST/ALT (ratio of 1.5 to 2.5 and total increase <10-fold)
  o ↑↑ γGT
  o ↑ alkaline phosphatase (mild)

➢ Others
  o ↑↑IgA
  o ↑IgG, IgM

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyltransferase; MCV, mean corpuscular volume.

Modified from: Shah VH. *Mayo Clinic Gastroenterology and Hepatology Board Review* 2008: page 331 with permission.

Patients with acute alcoholic hepatitis often deteriorate during the first few weeks in hospital, with a mortality rate of 20-50%. The condition may take one to six months to resolve even with complete abstinence. Alcoholic hepatitis progresses to cirrhosis in 40% of clinical episodes. Bad prognostic indicators include spontaneous encephalopathy, markedly prolonged INR unresponsive to vitamin K and severe hyperbilirubinemia of greater than 350μmol/L. Both the discriminant function (see below) and the model for end-stage liver disease (MELD) score (Appendix 1) can be used to predict short-term mortality in patients with alcoholic hepatitis. Long-term survival in patients with alcoholic hepatitis who discontinue alcohol is significantly better than in those who continue to drink, although it remains considerably below that of an age-matched population. Three-year survival approaches 90% in abstainers, whereas it is less than 70% in active drinkers.
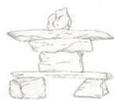
Table 3. Comparison of viral hepatitis and alcoholic hepatitis based on history and physical examination, laboratory tests and liver histology.

	Viral Hepatitis	Alcoholic Hepatitis
➢ History	o Risk factors	o Significant alcoholic intake
➢ Physical Examination	o Mild hepatomegaly o Extrahepatic stigmata not prominent	o Moderate to marked hepatomegaly o Florid stigamata
➢ Laboratory tests	o AST variable o ALT usually > AST	o AST <3 00 o often AST: ALT 2: 1 or more
➢ Liver histology	o Mononuclear cells o Portal tract centered o Ground glass cells (HBV) o Special stains (HBV) o Fat, esp. HCV	o Polymorphs o Pericentral, diffuse o Mallory's hyaline o Macrovesicular fat

5. Alcoholic Cirrhosis

Established cirrhosis is usually a disease of middle age after the patient has had many years of drinking. Although there may be a history of alcoholic hepatitis, cirrhosis can develop in apparently well-nourished, asymptomatic patients. Occasionally, the patient may present with end-stage liver disease with malnutrition, ascites, encephalopathy and a bleeding tendency. A history of alcohol abuse usually points to the etiology. Clinically, the patient is wasted. There may be bilateral parotid enlargement, palmer erythema, Dupuytren's contractures and multiple spider nevi. Males develop gynecomastia and small testes. Hepatomegaly is often present, affecting predominantly the left lobe due to marked hypertrophy and there are signs of portal hypertension including splenomegaly, ascites and distended abdominal wall veins. At the late stage, the liver may become shrunken and impalpable. There may be signs of alcohol damage in other organ systems such as peripheral neuropathy and memory loss from cerebral atrophy. Alcoholic cirrhosis is also associated with several renal problems. These include lgA nephropathy, renal tubular acidosis and the development of hepatorenal syndrome. There is an association between viral hepatitis B & C and alcoholic cirrhosis.

The diagnosis of alcoholic cirrhosis rests on finding the classical signs and symptoms of end-stage liver disease in a patient with a history of significant alcohol intake. Liver biopsy is encouraged, especially when the diagnosis is in question, since patients usually under report the amount of alcohol consumed. In addition to confirming the diagnosis, liver biopsy is also useful for ruling out other unsuspected causes of liver disease, better characterizing the extent of the damage, providing prognosis, and guiding therapeutic decision making.

Histologically, the cirrhosis is micronodular. The degree of steatosis is variable and alcoholic hepatitis may or may not be present. Pericellular fibrosis around hepatocytes is widespread. Portal fibrosis contributes to the development of portal hypertension. There may be increased parenchymal iron deposition. When marked, genetic hemochromatosis has to be

excluded. With continued cell necrosis and regeneration, the cirrhosis may progress to a macronodular pattern.

Biochemical abnormalities include a low serum albumin, elevated bilirubin and aminotransferases. AST and ALT levels rarely exceed 300U/L and the AST/ALT ratio usually exceeds 2. γGT is disproportionately raised with recent alcohol ingestion and is a widely used screening test for alcohol abuse. With severe disease, the INR may be prolonged. Portal hypertension results in hypersplenism leading to thrombocytopenia, anemia and leukopenia. Other non-specific serum changes in acute and chronic alcoholics include elevations in uric acid, lactate and triglyceride, as well as reductions in glucose, potassium, phosphate and magnesium.

The prognosis of alcoholic cirrhosis depends on whether the patient can abstain from alcohol, this in turn is related to family support, financial resources and socio-economic state. The presence of hepatitis also influences prognosis. Patients who abstain have a five-year survival rate of 60 to 70%, which falls to 40% in those who continue to drink. Women have a shorter survival than men. Bad prognostic indicators include low serum albumin concentration, increased INR, low hemoglobin, encephalopathy, persistent jaundice and azotemia. Zone 3 fibrosis and perivenular sclerosis are also unfavourable features. Complete abstinence may not improve prognosis when portal hypertension is severe, although at the earlier stage of cirrhosis, the portal pressure may actually fall with abstinence. Hepatocellular carcinoma occurs in 10% of stable cirrhotics and the incidence is higher in patients who also have viral hepatitis infection. This usually develops after a period of abstinence and macronodular cirrhosis is present. Treatment strategies can be instituted if detected early (see below), therefore long-term follow-up and periodic screening is advisable.

5.1. Management

Early recognition of alcoholism is important (Table 4). Physicians should have a high index of suspicion when a patient presents with anorexia, nausea, diarrhea, right upper quadrant tenderness and an elevated γGT. The most important therapeutic measure is total abstinence from alcohol. As patients can rarely achieve complete and durable abstinence from alcohol without assistance, support groups and regular follow-up is needed to reinforce the need for abstinence. Referral to a drug dependency unit is appropriate. Withdrawal symptoms should be treated with a benzodiazepine. A nutritious well balanced diet with vitamin supplements should be instituted. In general, enteral nutrition is preferable over parenteral supplementation, and protein should be supplied to provide positive nitrogen balance. Nutritional supplementation is generally associated with an improvement in liver test results, but only rarely with a mortality benefit.

Table 4. Treatment of Alcoholic Liver Disease

- Early recognition and treatment of alcoholism
- Complete alcohol abstinence
- Nutritional support to correct any associated malnutrition
- Treatment of liver complications—ascites, encephalopathy, esophageal varices
- Glucocorticosteroids for severe alcoholic hepatitis complicated by hepatic encephalopathy
- Pentoxifylline—reduces incidence of new-onset type 4 hepatorenal syndrome and 1 month mortality rate
- No proven use for PTU, anabolic androgenic steroids, hepatotrophic agents (insulin, glucagon)

Alcoholic fatty liver responds to alcohol withdrawal and a nutritious diet. The histological changes will revert back to normal in approximately 6 weeks. However, with long-term follow-up, patients with fatty liver disease may develop fibrosis or even cirrhosis as the liver heals. Morphologic features predictive of progression to fibrosis, cirrhosis, or both include severe steatosis, giant mitochondria, and the presence of mixed macrovesicular/ microvesicular steatosis.

Patients with severe alcoholic hepatitis should be admitted to hospital and complications of liver failure treated appropriately. Specific treatments for alcoholic hepatitis include the use of corticosteroid (40 mg/day for 4 weeks and then taper). Recent meta-analyses of thirteen randomized controlled trials showed a significant benefit of steroids for patients with severe alcoholic hepatitis complicated by hepatic encephalopathy (HE). There is reduction of the short-term mortality of about 50% in patients with severe alcoholic hepatitis. A discriminant function of >32 is a predictor of poor prognosis and favorable response to corticosteroid therapy. Discriminant function = 4.6 X (prothrombin time - control prothrombin time) in seconds + serum bilirubin in μmol/L $\div$ 17. Patients with gastrointestinal hemorrhage, active infection, diabetes and acute pancreatitis tend to do worse with corticosteroid, and therefore should not be considered for it in the setting of severe alcoholic hepatitis. A liver biopsy is needed to confirm the presence of severe alcoholic hepatitis before corticosteroid administration.

Propylthiouracil has been used to dampen the hepatic hypermetabolic state in alcoholic hepatitis. In one long-term randomized controlled trial, there was a significantly reduced two-year mortality rate in patients who continued to drink moderately. Those who were abstinent from alcohol did not derive any benefits. However, other investigators have not been able to reproduce these positive results. A systematic review of more than 700 patients from six published randomized, controlled trials has failed to show any effect of propylthiouracil on mortality, individual laboratory parameters, liver histology, or liver related complications. Therefore, current evidence cannot support the routine use of propylthiouracil in acute alcoholic hepatitis.

Testosterone and anabolic androgenic steroids have been tried with conflicting results, Intravenous amino acid supplements have been given to the severely protein malnourished with varying degrees of success. Their expense cannot justify their use in every patient with alcoholic hepatitis. Infliximab, an anti-tumor necrosis factor alpha (TNF-α) antibody, theoretically could dampen the inflammatory process in alcoholic hepatitis. Two recent trials showed that the patients with alcoholic hepatitis treated with infliximab had more infectious complications without any benefit in liver function or Maddrey scores. The only randomized controlled study to date has demonstrated a higher probability of death at 2 months in those patients randomized to steroids and infliximab.

Pentoxifylline, an anti-inflammatory agent with anti-TNF-α properties, has been shown in one study to reduce the incidence of new-onset type 1 hepatorenal syndrome and mortality at 1 month. Pentoxifylline is safe and cheap, and could be used despite the lack of a confirmatory study. Insulin and glucagons are both hepatotrophic agents. Their use in alcoholic hepatitis could theoretically improve hepatic regeneration. However, patients treated with both agents have had complications and even deaths from hypoglycemia. Therefore, these agents should not be used except in the setting of a clinical trial.

Finally, it must be stressed that a good nutritional intake is necessary to hasten recovery and improve survival. At 1 year from the time of diagnosis of alcoholic hepatitis, patients with

mild malnutrition have a 14% mortality rate, compared with a 76% mortality rate in those with severe malnutrition.

Patients who have established alcoholic cirrhosis need to be monitored for complications of cirrhosis in the same way that any other patient with cirrhosis is being monitored. Periodic assessments should include a surveillance gastroscopy to check for the presence of esophageal varices and prophylactic β-blocker therapy instituted for those with large esophageal varices. The recent advent of a transjugular intrahepatic portosystemic stent shunt (TIPS) has replaced a surgical portocaval shunt as the treatment of choice for uncontrolled bleeding esophageal varices, although the mortality rate is very high in those patients with acute alcoholic hepatitis. Hepatic encephalopathy remains a complication, but usually can be controlled with prophylactic lactulose. Ascites is managed with a low sodium diet and diuretic therapy. Ascites frequently settles down in those patients who abstain from alcohol for more than 6 months. In those patients who ascites becomes refractory to diuretic therapy, TIPS should be considered as a treatment option, especially in those patients who have been abstinent from alcohol for more than 6 months. Every effort should be made to exclude spontaneous bacterial peritonitis and prevent hepatorenal syndrome, two life threatening complications of ascites. Periodic screening for the presence of hepatoma should be made, since effective treatments are available if hepatomas are detected early. Surgical resection in the stable compensated cirrhotic patient or local ablative therapy such as intra-lesional radiofrequency ablation in the mildly decompensated patient should be offered.

Those patients who are also infected with viral hepatitis B or C should be assessed for their suitability to receive anti-viral therapy. It is preferable that patients totally abstain from alcohol during the treatment period. Untreated viral hepatitis can certainly accelerate the fibrotic process in alcoholic cirrhosis. Colchicine has been tried as an antifibrotic agent to reduce the extent of cirrhosis and hence portal pressure without much success. Liver transplantation is a treatment option for patients with end stage alcoholic cirrhosis and this is the treatment of choice in the patient with decompensated alcoholic cirrhosis. Ethical issues surrounding the use of such a scarce resource for a self inflicted disease still need to be settled, especially when it relates to liver transplantation for patients who have active alcoholic hepatitis. In the centres that transplant alcoholic cirrhosis, the results are comparable to those in patients with other forms of cirrhosis.

Appendix 1
MELD (Model for End Stage-Liver Disease) Score
MELD Score = [0.957 X log (serum creatinine in mg/dL) + 0.378 X log (serum bilirubin in mg/dL) + 1.120 X log(INR) + 0.643] X 10
If patient is receiving dialysis, the serum creatinine is set to 4.0
Web link: www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older

Chapter 19: Autoimmune Hepatitis
A. J. Montano-Loza.

1. Introduction

Autoimmune hepatitis (AIH) is a disease characterized by chronic inflammation of the liver, interface hepatitis on histologic examination, hypergammaglobulinemia, and production of autoantibodies. AIH results from the development of an immune response against normal self-antigens that disrupt the immune regulatory system (Krawitt 2006). This disease has a global occurrence, and the prevalence among Caucasian northern Europeans is 17 cases per 106 persons per year. In North America the frequency of AIH among patients with chronic liver disease is between 11% and 23% (Boberg 2002).

Two types of AIH are recognized based, on serological markers and clinical phenotypes. Type 1 AIH is the most common form worldwide, constituting 80% of all cases. It is characterized by the presence of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). Eighty percent of patients are female, and occurs as commonly across all age ranges. Approximately, 40% of affected individuals have concurrent immune diseases, mainly autoimmune thyroiditis, synovitis or ulcerative colitis. Type 2 AIH is characterized by the presence of antibodies to liver/kidney microsome type 1 (anti-LKM1). This disease occurs mainly in children, and concurrent immune disease are also common, especially type 1 diabetes mellitus, vitiligo, and autoimmune thyroiditis (Manns 2010).

2. Diagnosis

Early symptoms of AIH are fatigue and arthralgia, but up to a third of patients are asymptomatic at diagnosis. Acute severe or even fulminant AIH is characterized by newly developed, severe inflammation in the liver, or a spontaneous exacerbation of a previously unsuspected chronic disease. AIH is typically diagnosed by demonstrating the presence of smooth muscle antibodies (SMA), antinuclear antibodies (ANA), or antibodies to liver-kidney microsome (anti-LKM) type 1 in patients in whom other diagnoses have been excluded (Czaja 2010).

3. Histologic Features

Liver biopsy is recommended to establish the diagnosis of AIH, and to guide treatment. Figure 1. illustrates a normal portal triad and the limiting plate. Interface hepatitis is defined as "portal inflammation crossing the limiting plate" (the first line of hepatocytes surrounding the portal triad), and is the histological hallmark of AIH. Lobular lymphoplasmacytic infiltration is also typical (Figure 2) but neither histological finding is specific for AIH, the absence of plasma cells in the infiltrate does not exclude the diagnosis.
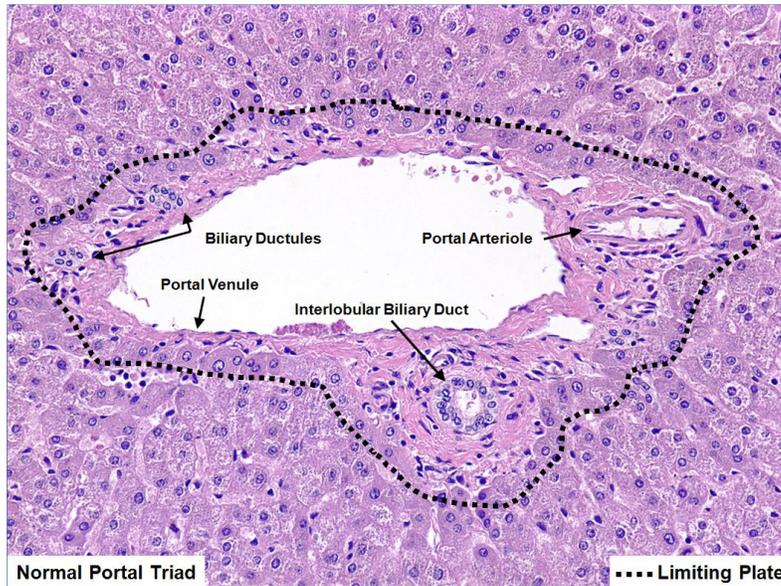
Figure 1. Normal portal triad and the limitant plate with delimitation of the first line of hepatocytes that surround the portal triad, denominated limiting plate.
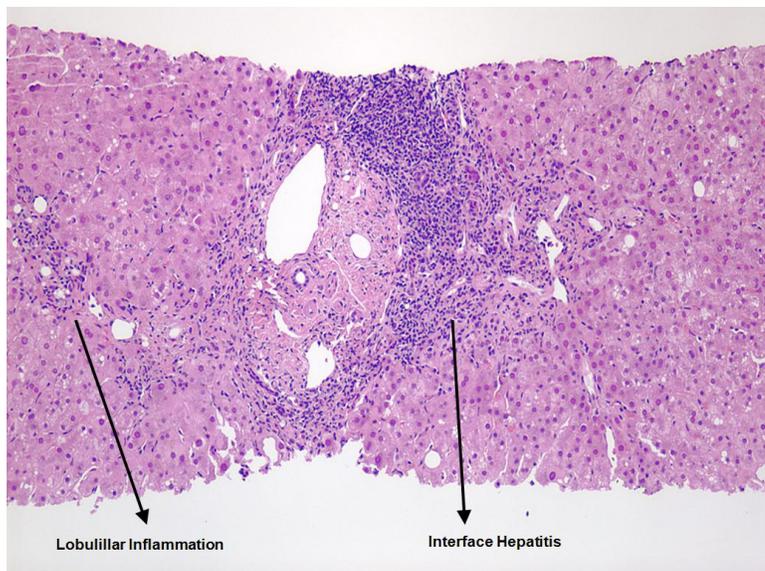
Figure 2. Characteristic liver biopsy changes in AIH, including interface hepatitis and lobular inflammation (Lymphoplasmacytic Infiltrate).

Two diagnostic scoring systems (a comprehensive system and a simplified system) have been developed by the International AIH Group that aid in the diagnosis of difficult cases. The simplified scoring system is easier to use in the clinic and assesses only 4 factors (Table 1) (Hennes 2008).

Table 1. Simplified Diagnostic Criteria for Autoimmune Hepatitis (AIH)

Variable	Cutoff	Points
o ANA or SMA	≥ 1:40	1
➢ ANA or SMA or LKM1	≥ 1:80 ≥ 1:40	2*
o IgG	>Upper normal limit >1.10 times upper normal limit	1 2
➢ Liver Histology (evidence of hepatitis is a necessary condition)	Compatible with AIH (chronic hepatitis with lymphocytic infiltrate, and no other characteristic findings)	1
	Typical AIH (interface hepatitis, portal lymphocytic or lymphoplasmacytic infiltrate through the lobule, [†]emperipolesis and rosettes of hepatocytes)	2
➢ Absence of viral hepatitis	Yes	2
		≥ 6: probable AIH ≥ 7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points). AIH= autoimmune hepatitis; ANA= antinuclear antibodies; SMA= smooth muscle antibodies.
[†]Emperipolesis: Active penetration by one cell into a larger cell, in this case when a lymphocyte penetrates a hepatocyte. (Adapted from Hennes 2008).

4. Treatment: Endpoints, Outcomes, and Liver Transplantation

The indications for treatment are based on the risk factors for disease progression, and for practical proposes can be classified as absolute, relative or uncertain indications, and no indications for treatment (Table 2) (Manns 2010). The relative contraindications for the use of prednisone or combination therapy of prednisone plus azathioprine in AIH are given Table 4. The preferred treatment schedule in adults with severe AIH is prednisone (prednisolone can be used in equivalent doses) in combination with azathioprine (50 mg/day generally used in North America and 1-2 mg/kg/day in Europe) (Table 2). Prednisone alone in a higher dose is as

effective as the combination regimen, but it is associated with a greater frequency of drug-related side effects. The dose of prednisone may be slowly tapered to the lowest individual level sufficient to maintain remission from prednisone 20 mg daily onwards, reduction should be done at the rate of 5 mg every week, until 10 mg per day is being given; an even further reduction by 2.5 mg per week may be used, down to 5 mg daily (Montano-Loza 2007).

Table 2. Treatment Indications for Adult Patients with Autoimmune Hepatitis (AIH)

Findings	Indications		
	Absolute	Relative	None
➤ Clinical	o Incapacitating symptoms o Relentless clinical progression o Fulminant presentation	o Mild or no symptoms	o Asymptomatic with mild laboratory changes o Previous intolerance of prednisone and/or azathioprine
➤ Laboratory	o AST≥10-fold normal o AST≥5-fold normal and γ-globulin≥2-fold normal	o AST 3-9 fold normal o AST≥5-fold normal and γ-globulin<2-fold normal	o AST<3-fold normal o Severe cytopenias o (White blood cell count below 2.5×10^9/L or platelet count below 50×10^9/L)
➤ Histologic	o Bridging necrosis o Multiacinar necrosis	o Interface hepatitis	o Inactive cirrhosis o Focal interface hepatitis o Portal hepatitis o Decompensated inactive cirrhosis with variceal bleeding or hepatic encephalopathy

AST = serum aspartate aminotransferase level.

(Adapted from Montano-Loza 2007).

Therapy should continue until remission, treatment failure, incomplete response, or drug toxicity. The average duration of treatment required for disappearance of symptoms, normalization of laboratory indices, and histological resolution is 22 months. The ideal end point of therapy in patients with AIH is resolution of all clinical, laboratory, and histological manifestations of disease activity. Approximately 80% of treated patients achieve remission criteria within 3 years. The life expectancies of treated patients exceed 85% at 10-years, and 74% at 20 years.

Liver transplantation is an effective treatment for the decompensated patient with AIH. Patient and graft survival after liver transplantation ranges from 83% to 92%. The actuarial 10-year survival of AIH after liver transplantation is around 75%. Recurrence of AIH in the

transplanted liver occurs in 20% of patients after 5 years, especially in individuals receiving inadequate immune suppression. Adjustments in the immunosuppressive regimen are usually able to suppress recurrent AIH, and infrequently cirrhosis or graft failure occurs (Montano-Loza 2009).

Table 3. Treatment Schedules for Adults Patients with Autoimmune Hepatitis Recommended by the AASLD

Weeks Administered	Combination Therapy*			Prednisone Therapy
	Prednisone (mg daily)	Azathioprine NA (mg daily)	EU (mg/kg/day)	Prednisone (mg daily)
1	30	50	1-2	60
1	20	50	1-2	40
2	15	50	1-2	30
Maintenance until end point Relative Contraindications	10	50	1-2	20

AASLD: American Association for the Study of the Liver Diseases. NA: North America; EU: Europe. (*Adapted from Montano-Loza AJ 2007*).
*preferred treatment schedule for AIH.

Table 4. Relative contraindications of Prednisone or combination therapy of Prednisone plus Azathioprine for adult patients with autoimmune Hepatitis

- o Cytopenias
- o Pregnancy
- o Active malignancy
- o Short course (less than 6 months)
- o Thiopurine methyltransferase deficiency
- o Post-menopausal state
- o Osteoporosis
- o Diabetes
- o Hypertension
- o Obesity
- o Emotional lability

Chapter 20: Primary Biliary Cirrhosis

A. L. Mason and B. Sis

1. Epidemiology

The term, primary biliary cirrhosis (PBC) was coined in 1949 but a similar condition was first described by Addison and Gull a hundred years prior in 1851. The terminology is not completely accurate, however, as the histological appearance is typically a chronic non-suppurative cholangitis (Figure 1), whereas only a proportion of patients develop cirrhosis. PBC is characterized by granulomatous destruction of 30 to 80 μm interlobular bile ducts that processes through four stages to cirrhosis. It is considered a pluriglandular disease as other organs are affected, such as the pancreas, salivary and lachrymal glands.

PBC has a worldwide distribution and has been found in all races. The prevalence of PBC ranges from 1:2,500 to 1:100,000 with an increasing prevalence moving North from the equator (Table 1).

Table 1. Demography of PBC

- o   Worldwide prevalence ranges from1 to 2,500 to more than 1 in 100,000
- o   Highest prevalence in Northern Europe and Canada
- o   As high as 1 in 500 in middle aged women
- o   Disease rarely reported in Sub-Saharan Africa.
- o   Ten fold increased prevalence of PBC with a first degree relative with PBC
- o   More prevalent in mono than dizygotic twins
- o   Prevalence increases with migration from low to high prevalence areas
- o   Clustering of disease in specific regions

In Canada, up to 1 in 700 middle-aged women develop PBC and in Northern Europe it is reported to be approximately 1 in 500 in specific locations. In British Columbia, there is an increased prevalence of disease in coastal First Nation populations, who are 3 times as likely to undergo liver transplantation for PBC compared to other Canadians. There also appears to be geographical clustering of disease in Europe and in one instance, this was related to specific water supply. It has been suggested that there is an increased prevalence of PBC near toxic waste sites suggesting a role for xenobiotics in the disease process. Generally speaking, PBC is predominantly found in the middle class population with a higher income and education status in North America, making it less likely that pollution plays a major role on disease.

Like other autoimmune disorders, PBC predominantly occurs in women with a ratio of 9 females for every male with disease. The reason for the female predilection is unknown but hormone replacement and younger age of first pregnancy are associated with increased risk of disease. These data are in keeping with the biology of one of the environmental agents linked with PBC, namely a betaretrovirus that is activated by pregnancy and female hormones in an animal model. Lesions in the X chromosome have been related to PBC as well. Notably, a higher frequency of monosomy secondary to X chromosome inactivation is found in PBC patients in general and a high prevalence of PBC has been reported in patients with Turner's syndrome.

2. Etiology

2.1. Autoimmune factors

PBC is considered an autoimmune disease because approximately 95% of patients make the diagnostic anti-mitochondrial antibodies (AMA) to pyruvate dehydrogenase E2 protein, referred to as the M2 antigen. The reason why patients make AMA is unknown but a protein resembling pyruvate dehydrogenase E2 is aberrantly expressed on the cell surface of diseased

biliary epithelium and in the macrophage/monocyte population in lymphoid tissues. Normally these proteins sequestered in the inner mitochondria and are therefore not encountered by the immune system. It is thought that the exposure of the pyruvate dehydrogenase E2 complex proteins may be one of the triggers that induce a loss of tolerance to mitochondrial proteins in the setting of an inflammatory response to diseased biliary epithelium. While the mechanism that misdirects the mitochondrial proteins to the cell surface is poorly understood, there are some exciting studies that suggest an environmental factor can elicit this disease specific mitochondrial phenotype. For example, co-culture studies have shown that a transmissible agent in the lymph nodes of patients with PBC can trigger a similar mitochondrial phenotype of PBC with increased and aberrant expression of mitochondrial antigens in healthy biliary epithelium.

There are several factors that suggest an autoimmune etiology of PBC. These include the formation of a humoral and cellular immune response to self-proteins as well as the association of PBC with other autoimmune disease. For example, patients with PBC have a higher risk of developing systemic lupus erythematosus, autoimmune thyroid disease, Raynaud syndrome, Sjögren syndrome and scleroderma (Table 2). There is also an increased risk of family members developing PBC and the related autoimmune diseases. However, the role that autoimmunity plays in causing bile duct damage is unknown (Table 3). Although of diagnostic utility, AMA do not appear to directly cause PBC, as patients without AMA have comparable disease, the titers do not correlate with activity and some AMA positive individuals have no disease. Furthermore experimental criteria for the establishment of PBC as an autoimmune disease have not been met as animal models inoculated with adjuvant and the mitochondrial antigen merely develop AMA without biliary disease. With regard to disease management, the autoimmune model has not served well for PBC in contrast to other disorders. In patients with autoimmune hepatitis, for example, the use of immunosuppression improves morbidity and mortality, whereas the use of specific immunosuppressive therapies for PBC patients is not recommended due to untoward toxicity and lack of efficacy.

Table 2. Diseases Associated with PBC (Gershwin 2005)

- ➤ Raynand's Disease (12%)

- ➤ Autoimmune thyroid disease (9%)

- ➤ Sjögren Syndrome (10%)

- ➤ Keratoconjunctivitis sicca: > 80%

- ➤ Systemic Lupus Erythematosus (3%)

- ➤ Scleroderma (2%)

- ➤ History of
    - o UTI (59%) vs. controls (52%)
    - o Cholecystectomy (27%) vs. controls (17%)
    - o Urinary tract infection (59%) vs. controls (52%)

Note: The approximate frequency of associations is shown in brackets.

Table 3. Factors indicative of an infectious versus autoimmune etiology of PBC (Mason 2002)

➤ Autoimmune:
  o Personal history and family history of other autoimmune disorders
  o Demonstrable cellular and humoral autoimmune response to mitochondrial and nuclear antigens but
    - Patients without AMA have similar disease process
    - Some patients with AMA do not develop disease
    - Immunosuppression therapy of little benefit

➤ Infectious:
  o Spouses, unrelated family members and care providers can develop PBC
  o PBC recurs in up to a third of patients after liver transplantation
  o Infectious agents in PBC patients' lymph nodes have been shown to trigger the mitochondrial phenotype of disease *in vitro*

2.2. Genetic factors

PBC is considered a complex disease as multiple factors impact on the development of disease. It is currently thought that an environmental agent triggers disease in genetically susceptible individuals. The disease is more frequently observed in monozygotic as compared to dizygotic twins and there is a ten fold increased prevalence of PBC in first degree relatives. Multiple studies have linked specific innate and adaptive immune system genes with PBC (Table 4). Three genome wide association studies involving more than 5,000 patients have confirmed an important association with the HLA class II region and the interleukin-12 (IL-12) cytokine axis with PBC. Of note, many of these genes associated with PBC have been found to confer risk to other autoimmune diseases as well (Table 4). These data suggest that PBC patients may be predisposed to a global disturbance in host response to microbial infections.

Table 4. Genetic Factors associated with PBC and other autoimmune disorders

➤ HLA class II region [DR, DQ]

➤ Innate immune system
  o *MBL* (mannose-binding lectin) – receptor for bacteria, viruses and parasites
  o *VDR* (vitamin D receptor) – associated with Grave's disease and susceptibility to mycobacteria tuberculosis
  o *NRAMP-1* (natural resistance-associated macrophage protein 1) – associated with resistance to bacterial and other infections
  o *C4*Q0, C4B*2* – (Complement 4) - associated with autoimmune hepatitis
  o *IRF5* (interferon regulatory factor 5) – associated with SLE, IBD, RA

➤ Adaptive immune system
  o *IL-12, IL-12 receptor* and *STAT4* (Cytokine axis stimulating T lymphocytes and natural killer cells to produce tumor necrosis factor α and interferon γ) - STAT 4 associated with SLE

- *CTLA-4* (Cytotoxic T-lymphocyte associated antigen 4) – associated with Celiac disease, type 1 diabetes
- *SPIB* (B-cell receptor signaling)
- *IKZF3* (regulates B cell activation) - associated with a lupus-like syndrome.
- *MMEL1* (membrane metallo-endopeptidase–like 1) - associated with RA and Celiac disease

2.3. Environmental factors

Spouses, unrelated family members and care providers have been reported to develop PBC, implicating environmental factors in disease. Moreover, migration studies show that children develop the relative incidence of their adopted host country. Observations from liver transplantation suggest that a transmissible factor is associated with the development of PBC. While 70% of recipients continue to have AMA in serum following transplantation, histological evidence for recurrent PBC is observed in up to 30% with immune destruction of bile ducts 10 years after liver transplant. Indeed, more potent immunosuppressive regimens accelerate the onset and severity of recurrent disease.

There is a controversy surrounding environmental agents that impact on the disease process. Several bacteria, xenobiotics and a betaretrovirus have been implicated in the etiology and pathogenesis of PBC but there is little direct evidence that any of these environmental factors causes PBC at this time. Cigarette smoking is the only xenobiotic clearly associated with PBC, albeit in a non-etiological role. Smoking cigarettes aggravates PBC, as the cumulative number of cigarette packs smoked is associated with advanced histological disease; however, patients with PBC tend to smoke less cigarettes and drink less alcohol as compared to the general population.

Patients with PBC are also more likely to suffer from recurrent urinary tract infection. Many bacteria have evolutionary conserved pyruvate dehydrogenase proteins that closely resemble mammalian mitochondrial proteins. As a result, it has been suggested that bacteria trigger AMA production by molecular mimicry. However, this mechanism has not been convincingly demonstrated in patients with PBC or any other human autoimmune disorder for that matter.

The identification of a betaretrovirus in patients with PBC is controversial. Two groups have been unable to confirm the preliminary findings in liver samples using different methods and the association is questionable because the virus is mainly detected in the lymphoid system. The connection of betaretrovirus with PBC is interesting because infection is associated with aberrant pyruvate dehydrogenase E2 protein expression. For example, the betaretrovirus is detected in lymph nodes of PBC patients in cells with the abnormal mitochondrial protein distribution. In addition, co-culture studies have shown that betaretrovirus can trigger the mitochondrial phenotype in healthy biliary epithelium *in vitro*.

3. Diagnosis

The diagnosis of PBC is usually established by evaluation of patients with elevated alkaline phosphatase and γ-glutamyl transferase for evidence of serum AMA reactive to M2 (Table 5). AMA are highly specific for PBC but are rarely detected in patients with SLE as well. A proportion of patients develop elevated serum IgM levels and make anti-nuclear antibodies (ANA). The ANA may be predictive of prognosis. For example, 25% of PBC patients make ANA that display a nuclear rim pattern with immunofluorescence; these antibodies react to

components of the nuclear envelope and pore complex, such as Gp210. Detection of ANA to Gp210 have been consistently associated with worse prognosis and liver failure. Anti-centromere antibodies are usually found in patients with the limited cutaneous disease associated with systemic sclerosis. A variable 10%-35% of patients with PBC reportedly make anti-centromere antibodies as well, which are associated with development of CREST syndrome as well as progressive liver disease.

Table 5. Presentation and diagnostic features of PBC

- ➢ Elevated alkaline phosphatase (screening)

- ➢ Symptom complex:
  - o Fatigue
  - o Pruritus
  - o Sicca syndrome
  - o Jaundice

- ➢ Anti-mitochondrial antibody to M2, increased serum IgM and ANA

- ➢ Liver biopsy evidence of non-suppurative granulomatous cholangitis
  - o Lack of extra-hepatic disease by cholangiography

- ➢ Differential diagnoses
  - o Primary sclerosing cholangitis
  - o Pericholangitis (small duct disease)
  - o Sarcoidosis
  - o Non-inflammatory idiopathic adulthood ductopenia
  - o Transplant related ductopenia
    - Acute cellular rejection
    - Graft versus host disease

Liver biopsy plays less of a role in diagnosis of PBC now that specific AMA to M2 are readily available and MRCP can effectively rule out large bile duct disease. The histological appearance of granulomatous destruction of bile ducts (Figure 1) is highly suggestive of PBC but may rarely be seen in patients with viral hepatitis, primary sclerosing cholangitis or autoimmune hepatitis. The liver biopsy can also be helpful in management of disease with atypical presentation, such as AMA negative patients, or unusual biochemical profiles suggestive of a hepatitis predominant presentation with elevated serum aminotransferase levels greater than 5 times the upper limit of normal. Histological stage is predictive of survival in PBC but it should be remembered that different histological stages can be observed in the same liver (Table 1).
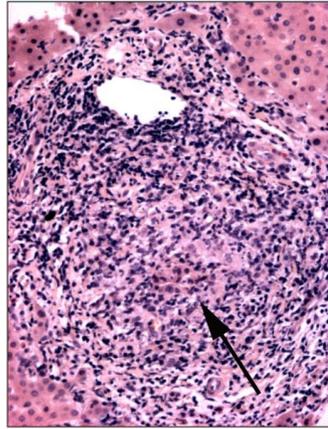
Figure 1. PBC liver biopsy showing granulomatous destruction of an interlobular bile duct (arrow).

An anatomical assessment of the liver is necessary with ultrasound or other modality and a cholangiogram with MRCP should be entertained if the diagnosis of PBC is uncertain. As discussed, the liver biopsy is necessary for establishing diagnosis of PBC in patients that lack AMA. AMA negative PBC used to be referred to as autoimmune cholangitis but now is thought to be in a diagnostic continuum with PBC. Patients presenting with the so-called "overlap syndrome" have features of both autoimmune hepatitis with markedly elevated serum aminotransferase levels and PBC. As PBC is an exclusion criteria for autoimmune hepatitis by definition, it is preferable to consider these patients as having a *forme fruste* or "hepatitis predominant" of PBC, as they usually end up with ductopenia and may also have the mitochondrial phenotype of PBC if tested. It is notable that hepatitis component may occur at presentation or remotely after diagnosis of PBC but an important diagnosis to make for management of the hepatitis component.

The differential diagnosis of PBC includes primary sclerosing cholangitis, which can be diagnosed by MRCP and pericholangitis associated with inflammatory bowel disease diagnosed by liver biopsy. Patients with sarcoidosis usually have parenchymal granuloma on biopsy and extrahepatic disease; however, the classical granulomatous destruction of bile ducts has been reported in a proportion of patients with sarcoid. The only other inflammatory ductopenic disorders of adulthood that share a histological similarity to PBC are acute cellular rejection and graft versus host disease. Otherwise, the idiopathic adulthood ductopenia syndromes lacking inflammatory disease have been reported in clusters and inbred populations attributable to genetic defects, as reported with the biliary transporter *ABCB4* gene linked with progressive familial intrahepatic cholestasis, for example.

4. Clinical presentation and management

Over the last 20 years, PBC has been diagnosed earlier in the clinical course and up to 50% of patients are asymptomatic. As the disease progresses, fatigue occurs in up to 80% of patients. Although low energy is a feature of many liver diseases, patients with PBC appear to experience additional problems such as exercise induced acidosis, autonomic neuropathy and

cardiomyopathy. Pruritis occurs in a range of 20% to 70% of patients with PBC and the severity may diminish over time. Sicca syndrome with either dry eyes or dry mouth is also common. Patients with PBC and CREST may suffer from Raynaud syndrome, cutaneous calcinosis, esophageal reflux and dysphagia.

Clinical trials with methotrexate, colchicine, prednisone and other immunosuppressive agents either lacked efficacy or showed undue toxicity. Therefore, PBC specific treatment is geared towards the pathophysiology of disease, where the progressive loss of bile ducts leads to accumulation of bile within the liver causing intra-hepatic damage. Accordingly, ursodeoxycholic acid has proven helpful as a water-soluble bile salt that acts as a choleretic to increase excretion of bile from the liver. Prior to the advent of UDCA therapy, the probability of progression to cirrhosis over 4 years with stage 1, stage 2 and stage 3 disease on initial biopsy was 31%, 50%, and 68%, respectively. Therefore, the average life expectancy at that time was approximately 12 years. With UDCA treatment, one third of patients normalize their liver function tests and a similar proportion develops sufficient benefit to avoid progression to liver failure. Survival rates with UDCA treatment have improved considerably and are estimated to be 85% at 10 years and 65% at 20 years.

Over a period of 15 to 20 years, the gradual loss of bile ducts results in fibrosis and then biliary cirrhosis. Variants of this clinical picture occur with severe ductopenia and repaid onset of marked cholestasis in 5% to 10% of patients. Another scenario occurs in a subgroup of PBC patients with features consistent with autoimmune hepatitis. In this case, patients experience ALT levels greater than 5-fold elevation of the upper limit of normal and have evidence of interface hepatitis on liver biopsy. Patients with this hepatitis predominant PBC have a worse prognosis compared to those with a typical course of PBC. They are an important subgroup to identify, as the hepatitis component may be responsive to immunosuppressive treatment.

Other management of PBC is directed towards symptomatic relief and prevention of other diseases as outlined on Table 7. Cholestyramine is the first line of treatment for pruritis but this should be taken at a 4-hour interval from UDCA therapy. Other measures such as opiate antagonists or rifampin are of help to patients that do not respond to cholestyramine. Furthermore, patients with severe pruritis may be candidates for plasmaphoresis or nasobiliary drainage. All patients with PBC are encouraged to take multivitamins, additional vitamin D and calcium for osteopenia. Regular bone scans are necessary to identify patients with progressive bone disease, which should be treated with alendronate 70mg per week. Statins are well tolerated and should be given to those with hypercholesterolemia.

PBC patients with cirrhosis should be screened for esophageal varices and hepatocellular carcinoma and those with progressive PBC and liver failure should be worked up for liver transplantation. Patients with PBC account for 10% of patients requiring liver transplantation in Canada and their outcomes are excellent. Even though disease may recur in up to 30% of patients after 10 years, this does not appear to have a demonstrable effect on mortality.

Table 6. Management of PBC

➢ Licensed therapy
  ○ UDCA 13-15mg/kg

➢ Anti-pruritic agents
  ○ Cholestyramine 4-8g BID, PRN
  ○ Rifampin 150-300mg BID, (potentially hepatotoxic)
  ○ Naltrexone 12.5mg slowly increased to 50mg/day, (potentially hepatotoxic)
  ○ Sertraline 75-100mg
  ○ Anti-histamines, (may cause worsening of sicca syndrome)

➢ Prevention of vitamin deficiency
  ○ Vitamin D 1,000 – 2,000 IU and Calcium 1-1.5g
  ○ Multi-vitamin

➢ Sicca syndrome
  ○ Artificial tears
  ○ Cyclosporine ophthalmic emulsion

➢ Hypercholesterolemia
  ○ Statins
  ○ Fenofibrate

➢ Liver failure
  ○ Liver transplantation

450
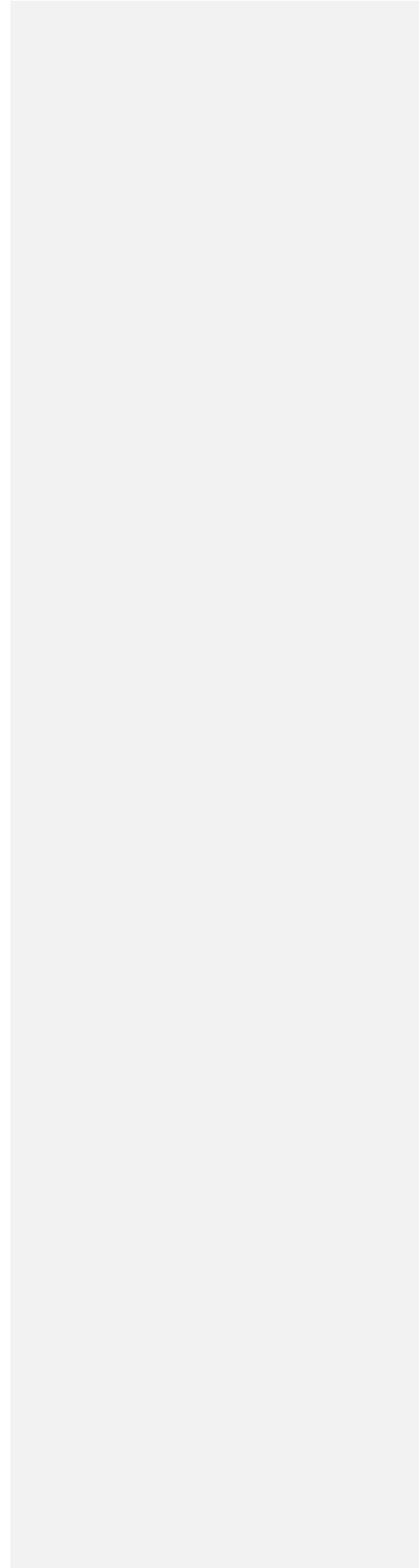
Chapter 21: Hemochromatosis and other Hepatic Iron-Storage Disorders
P. C. Adams
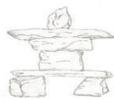
1. Definition

Hemochromatosis is an iron-storage disorder in which there is an inappropriate increase in the absorption of iron from the gut. This leads to iron deposition in various organs with eventual impairment, especially of the liver, pancreas, heart and pituitary. The term hemochromatosis is preferred for genetic hemochromatosis with other diseases associated with iron overload, referred to as secondary iron overload.

2. Genetics

The gene for hemochromatosis (*HFE*) on chromosome 6 was discovered in 1996. The HFE protein is similar to a MHC class-I protein. A genetic test for hemochromatosis has demonstrated that more than 90% of typical hemochromatosis patients have a C282Y mutation of the *HFE* gene. The presence of a single mutation in most patients is in marked contrast to other genetic diseases in which multiple mutations were discovered (cystic fibrosis, Wilson disease, alpha-1-antitrypsin deficiency). The C282Y mutation creates a conformational change in the HFE protein which normally interacts with the transferrin receptor 1 and 2, bone morphogeneic protein 6, hemojuvelin and hepcidin to regulate iron uptake.

A second minor mutation, H63D, was also described in the original report. Hemochromatosis is one of the most common genetic diseases, inherited as an autosomal recessive trait affecting one in 200 of the Caucasian population. Since genetic testing has been introduced, an increasing number of homozygotes have been described without iron overload. This incomplete penetrance of the gene may explain the discrepancy between the high prevalence in genetic studies and the clinical impression that hemochromatosis is an uncommon condition.

3. Clinical Manifestations

The homozygote may have continued iron accumulation leading to target organ damage. In hemochromatosis, the absorption of iron is inappropriate to the needs of the body, resulting in absorption of 4 mg/day or more. In advanced disease, the total body iron accumulation may be 40-60 g.

Most patients are asymptomatic until the 5th or 6th decade, at which time they can present with non-specific symptoms of arthritis, diabetes, fatigue or hepatomegaly (Table 1). Other symptoms include pigmentation of the skin (melanin deposition), impotence and dyspnea secondary to congestive heart failure. The classic triad of skin pigmentation, diabetes and liver disease (bronze diabetes) occurs in a minority of patients and is a late stage of the disease.

Table 1. Presentation of the Patient with Hemochromatosis

➢ Family History

➢ Chronic Liver Disease

➢ Hepatocellular Cancer

➢ Non-specific
  o Pigmentation of skin
  o Impotence
  o Dyspnea (secondary to CHF)
  o Diabetes

Abbreviation: CHF, congestive heart failure

The attribution of symptoms to hemochromatosis has become increasingly difficult since studies using control subjects without *HFE* mutations have shown a similar prevalence of non-specific symptoms such as fatigue, arthralgias, and diabetes.

4. Screening

A patient with suspected hemochromatosis or unexplained liver disease can be screened for the disease with a serum ferritin and transferrin saturation (serum iron/TIBC). Transferrin saturation has significant biological variability. These iron tests increase with age and are more abnormal in males than females because of the regular menstrual blood loss in women. Serum ferritin increases with body iron stores but is commonly elevated with fatty liver, daily alcohol consumption and chronic inflammation.

5. Diagnosis

The diagnosis of hemochromatosis was previously confirmed by liver biopsy, which demonstrates marked parenchymal iron deposition with iron staining of the tissue. This hepatocyte deposition of iron is to be distinguished from secondary (non-genetic) causes of iron-overload (Table 2), by the resence of excess iron deposition in the reticuloendothelial system. The hepatic iron concentration and the hepatic iron index (hepatic iron concentration/age) can be helpful in distinguishing genetic hemochromatosis from the increased iron overload that is seen in other chronic liver diseases such as alcoholic liver disease and chronic hepatitis C.

Table 2. Classification of the acquired iron overload syndromes

➢ Hematological disorders	o Iron-loading anemias o thalassemia major o sideroblastic anemia o chronic hemolytic anemia o ineffective erytheroporesis
➢ Chronic liver disease (end stage, cirrhosis)	o HCV, HBV o HCV porphyria, (porphyria cutanea tarda) o Alcoholic liver disease o NAFLD/NASH o Porta-caval shunt
➢ Increased iron intake	o Dietary iron overload (African iron syndrome)
➢ Parenteral iron overload	
➢ Longterm hemodialysis	o Mulitple blood transfusions (for example, for chronic hemolytic anemia)
➢ Acerloplasminemia	

MRI scanning can detect moderate to marked iron overload in the liver. Genetic testing has led to a re-evaluation of the role of liver biopsy in hemochromatosis and biopsy has moved from a diagnostic test done in most cases to a prognostic test done in selected cases with liver

dysfunction. C282Y homozygotes, detected as young adults with a serum ferritin < 1000 μg/L, a normal AST and without hepatomegaly, will not require a liver biopsy.

Genetic testing is particularly useful in the evaluation of a patient with other risk factors for iron overload such as alcoholic liver disease or viral hepatitis (Table 3). Hepatic elastography may be a new tool to detect liver fibrosis without the need for a liver biopsy.

Table 3. Interpretation of genetic testing for hemochromatosis

C282Y homozygote – This is the classical genetic pattern that is seen in > 90% of typical cases. Expression of disease ranges from no evidence of iron overload to massive iron overload with organ dysfunction. Siblings have a one-in-four chance of being affected and should have genetic testing. For children to be affected, the other parent must be at least a heterozygote. If iron studies are normal, false positive genetic testing or a non-expressing homozygote should be considered.

C282Y / H63D – Compound heterozygote – This patient carries one copy of the major mutation and one copy of the minor mutation. Most patients with this genetic pattern have normal iron studies. A small percentage of compound heterozygotes have been found to have mild to moderate iron overload. Severe iron overload is usually seen in the setting of another concomitant risk factor (alcoholism, viral hepatitis).

C282Y heterozygote – This patient carries one copy of the major mutation. This pattern is seen in about 10% of the Caucasian population and is usually associated with normal iron studies. In rare cases the iron studies are high in the range expected in a homozygote rather than a heterozygote. These cases may carry an unknown hemochromatosis mutation and liver biopsy is helpful to determine the need for venesection therapy.

H63D homozygote – This patient carries two copies of the minor mutation. Most patients with this genetic pattern have normal iron studies. A small percentage of these cases have been found to have mild to moderate iron overload. Severe iron overload is usually seen in the setting of another concomitant risk factor (alcoholism, viral hepatitis).

H63D heterozygote – This patient carries one copy of the minor mutation. This pattern is seen in about 20% of the Caucasian population and is usually associated with normal iron studies. This pattern is so common in the general population that the presence of iron overload may be related to another risk factor. Liver biopsy may be required to determine the cause of the iron overload and the need for treatment in these cases.

No HFE mutations – There will likely be other hemochromatosis mutations discovered in the future. If iron overload is present without any *HFE* mutations, a careful history for other risk factors must be reviewed and liver biopsy may be useful to determine the cause of the iron overload and the need for treatment. Most of these cases are isolated, non-familial cases. Genetic testing for new iron mutations in ferroportin, hepcidin, or hemojuvelin is not widely available.

The heterozygote individual may have normal or minor derangements in iron metabolism that have no clinical significance. A patient that carries both the major mutation (C282Y) and the minor mutation (H63D) is called a compound heterozygote. These patients may have mild to moderate iron overload but are often normal.

6. Treatment

The treatment of hemochromatosis involves the removal of excess body iron. Iron is best removed from the body by weekly or twice weekly phlebotomy of 500 mL of blood until the body iron stores are within normal limits. The duration of treatment varies with the age and sex of the patient but older males may require weekly venesections for over three years. A serum ferritin is measured every three months to assess progress and when the serum ferritin is in the low normal range (50 μg/L), the frequency of venesections is decreased to three or four per year. Not all patients will require maintenance therapy.

The goal of therapy is to prevent any further tissue damage. Unfortunately, many of the symptoms do not improve following iron depletion. The most common cause of death is liver failure and/or hepatocellular carcinoma once cirrhosis has become established. Siblings of the patient with hemochromatosis must be screened with serum
ferritin, transferrin saturation and genetic testing as the siblings have a one-in four chance of being affected. Genetic testing can now identify heterozygotes so the screening of a spouse with genetic testing can be helpful to predict the risk in children.

Screening of the general population for hemochromatosis has found many genetic mutations but not much clinical disease. Genetic screening has the potential to identify cases at birth but raises ethical issues such as genetic discrimination. Chelating agents such as desferoxamine (parenteral) and deferasirox (oral) are reserved for the patient with iron overload secondary to an iron loading anemia such as thalassemia. Future research is in progress to look for new genes that may cause iron overload, or may modify the clinical expression of hemochromatosis.
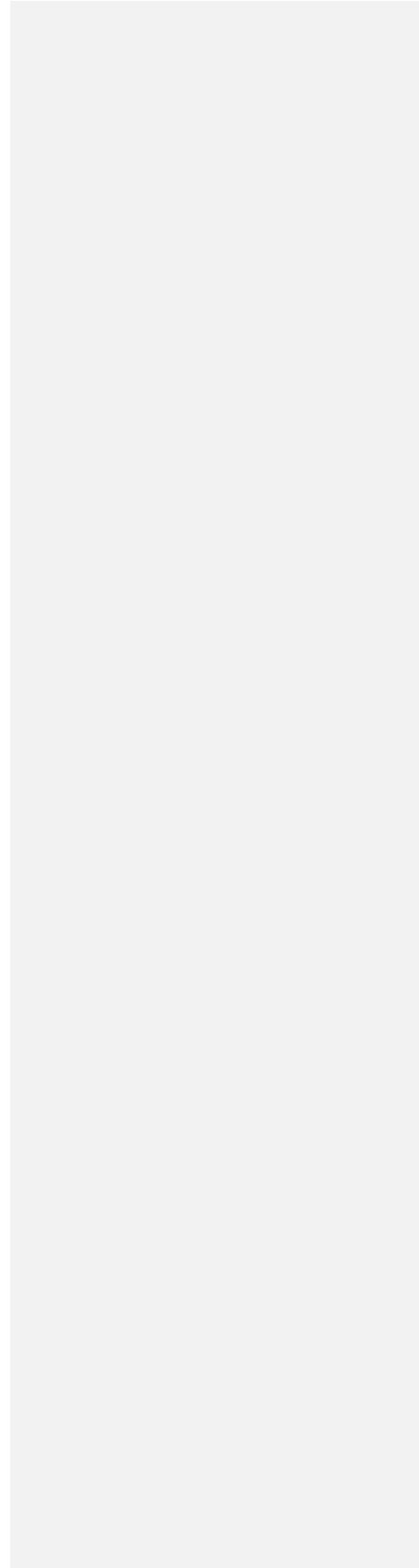
Chapter 22: Vascular Disorders in the Liver
C. S. Coffin

1. Introduction

The liver is a highly vascular organ; receiving 25% of cardiac output. Hence, it is highly vulnerable to circulatory disturbances causing diminished perfusion. There are a number of well-recognized forms of vascular injury to the liver. These include conditions related to underlying heart disease and hemodynamic instability such as congestive hepatopathy (also known as "cardiac cirrhosis") and ischemic hepatitis (or "shock liver"). Vascular injury may be related to a predisposing hypercoagulable state, leading to portal vein thrombosis (PVT). Finally, other more rare causes include sinusoidal obstruction syndrome (SOS, previously known as "hepatic venocclusive disease"), Budd Chiari Syndrome (BCS), hereditary hemorrhagic telangectasia, HHT, aka and Osler-Weber-Rendu [OWR] Syndrome. Table 1 provides a summary of the main clinical presentation and management of the five major vascular disorders of the liver.

Table 1. Summary of Major Vascular Disorders of the Liver

Disease	Clinical Presentation	Laboratory Tests	Diagnostic Imaging	Management
Ischemic Hepatitis	o Shock, right upper quadrant abdominal pain	o ALT and AST >1000. o Jaundice is rare	o Doppler US to rule out PVT and Hepatic Artery Thrombosis (HAT)	o Supportive care reverse hemodynamic instability
Congestive Hepatopathy	o Congestive Heart Failure, jaundice, tender hepatomegaly	o Moderate elevation in bilirubin and transaminases o High SAAG.	o Abdominal Imaging (CT), showing possible hepatomegaly and ascites	o Treat underlying heart disease
Portal Vein Thrombosis (PVT)	o Acute PVT - asymptomatic or sudden abdominal pain with SIRS. o Chronic - Portal hypertension, variceal bleeding	o Mildly abnormal liver function tests/enzymes.	o Doppler ultrasound showing reduced or absent flow. Chronic PVT – show collateral veins within main PV.	o Management of variceal bleeding and portal hypertension o Anticoagulation for 3- 6 months if acute PVT, and permanent in non-cirrhotic patients with pro-thrombotic condition

Table 1. Summary of Major Vascular Disorders of the Liver

Disease	Clinical Presentation	Laboratory Tests	Diagnostic Imaging	Management
Sinusoidal Obstruction Syndrome (SOS)	o Underlying risk factor (myeloablative conditioning), portal hypertension, sudden jaundice, ascites, tender hepatomegaly	o Nonspecific elevation of aminotransferases and conjugated bilirubin	o Ultrasound, o rarely liver biopsy o HVPG (>10 mm Hg)	o Supportive care, treatment of cause,
Budd-Chiari Syndrome (BCS)	o Asymptomatic, unexplained cirrhosis, fulminant liver failure. Presence of underlying risk factor, hypercoagulable disorder	o Nonspecific abnormality liver function tests, o High SAAG	o Doppler Ultrasound-- absent or turbulent flow in larger hepatic vein, with hepatic venous collaterals	o Supportive care, o Manage portal hypertension, anticoagulation to prevent recurrence if underlying pro-thrombotic condition. TIPS and transplant as last resort
Osler-Weber-Rendu Syndrome (Hereditary Hemorrhagic Telangectasia, HHT)	o Family history, mucocutaneous and GI bleeding (epistaxis)	o Elevation AP and GGT. Normal liver function	o Doppler Ultrasound or CT showing vascular malformations. Angiography is gold standard.	o Supportive care manage portal hypertension. Hepatic artery embolization in non-transplant candidates, liver transplant

Abbreviations: AP, alkaline phosphatase; HAT, hepatic artery; HVPG, hepatic vein pressure gradient; PVT, portal vein thrombosis; SAAG, serum ascites albumin gradient; SIRS, Systemic inflammatory response syndrome; thrombosis; TIPS, transjugular portosysmic shunt.

2. Ischemic Hepatitis and Congestive Hepatopathy

Ischemic hepatitis (or "shock liver") is a condition of acute hypoperfusion of the liver, usually due to shock or hypotension, resulting in diffuse hepatocyte injury. Ischemic hepatitis can also be due to thrombosis of the hepatic artery, such as in sickle cell crisis. The patient may present with right upper quadrant pain associated. Blood testing usually shows a profound elevation of liver transaminases from hepatocytes injury and leakage such that transmanise levels (aspartate aminotransferase, AST and alanine aminotransferase, ALT) may exceed 1000 U/L (normal limit is 60 U/L). Only acute viral hepatitis and acetaminophen injury is known to cause such a high elevation in these hepatic enzymes (reflecting hepatocellular damage). Jaundice can

occur, but is rare and transient. Liver pathology is characterized by Zone 3 injury of the hepatic acinus that can extend to mid-zonal areas with severe and prolonged ischemia. There are usually few inflammatory cells.

Ischemic hepatic often co-exists with congestive hepatopathy, and many of the clinical features are similar. Congestive hepatopathy refers to hepatic injury due to passive congestion from right-sided heart failure (i.e., due to constrictive pericarditis, triscupid regurgitation, cardiomyopathy). The diagnosis of congestive hepatopathy is suspected from the clinical presentation of right-sided heart failure, jaundice, and tender hepatomegaly. The liver biochemistries are non-specific, and show only modest abnormalities such as elevation in unconjugated hyperbilirubinemia, elevated aminotransferases (usually <2' to 3-fold), and prolonged PT/INR. The ascetic fluid (if present) has high albumin content and the serum ascites/albumin gradient (SAAG) is ($\geq$ 11 micromole/L). This liver disorder is more important as an index of the severity of heart failure than as diagnosis by itself, and management is focused on treating the underlying heart disease.

3. Acute and Chronic Portal Vein Thrombosis

Portal vein thrombosis (PVT) can be acute or chronic, and is usually caused by malignant invasion or thrombosis. Local risk factors are identified in only about one-third of patients, and include cirrhosis, cancer, focal inflammatory lesions, and injury to the portal venous system. These risk factors often occur in patients with a background history of an inherited or acquired pro-thrombotic condition. In young patients without a history of cancer or cirrhosis, acute PVT is often the first manifestation of an undiagnosed myleoproliferative disease.

Acute PVT usually presents with sudden onset abdominal pain, without peritoneal signs (except when an intra-abdominal inflammatory focus is the underlying causative event). Patients commonly manifest a marked systemic inflammatory response syndrome (SIRS), with persistent non-spiking fevers, abdominal pain and a transient rise in aminotransferases. Mesenteric thrombus progression can lead to intestinal ischemia, and if untreated can lead to severe persistent pain, bloody diarrhea, ascites and even peritonitis, shock, and multi-organ failure.

In chronic portal vein thrombosis (aka "portal cevernoma"), a network of collateral veins with hepatopetal flow connects the patent portion of the portal vein upstream from the thrombus, to the patent portion downstream. The degree of collateral flow varies from patient to patient, but complete occlusion is associated with the development of portal hypertension and portosystemic collaterals.

There are no RCTs (Randomized Controlled Trials) regarding the optimal treatment of acute PVT. Spontaneous recanalization is rare. Retrospective studies have shown that anticoagulation therapy is associated with improved rates of recanalization. It is generally recommended that at least 3 months of anticoagulation be given, and that permanent therapy be considered in patients with permanent prothrombotic conditions.

Diagnosis of PVT is usually made after first presentation of portal hypertension and hypersplenism. Gastrointestinal variceal bleeding is better tolerated, as patients are often younger with preserved liver function. Approximately 50% of patients hepatic encepatholopathy, and 10% present with hepatopulmonary syndrome. Liver enzymes are usually normal, with only mild alteration in coagulation factors. If a patient has biliary symptoms (i.e., jaundice, cholecystitis, pancreatitis), these may be due to portal cholangiopathy from compression of the large bile ducts.

The diagnosis of acute or chronic PVT is made by abdominal imaging. Ultrasound will show obstruction of the vessel lumen, with distention of the portal vein. Chronic PVT will show

replacement with serpiginous structures or collateral veins within the main portal vein. Doppler ultrasound of the vessels shows the absence or reduced flow within the vessel lumen. CT or MRI imaging with vascular contrast is recommended for assessment of thrombus extension, management since the mesenteric veins are difficult to visualize by ultrasound.

The management of chronic PVT is aimed at reducing the complications of portal hypertension such as esophageal variceal bleeding. Provided there is no major contraindication, anticoagulation should only be considered in non-cirrhotic patients with a known pro-thrombotic condition.

4. Sinusoidal Obstruction Syndrome

Sinusoidal Obstruction Syndrome (SOS) is a primary circulatory disorder due to obstruction of the hepatic sinusoids. In developed countries, SOS occurs most commonly as a complication of myeloablative conditioning regimens for hematopoietic stem cell transplantation, such as combination of high-dose chemotherapy and total body irradiation therapy. The overall incidence of SOS has declined in most centres with the use of reduced intensity conditioning regimens. SOS should be considered in persons at high risk for SOS such as those with a history previous of SOS, some forms of pre-existing liver disease (i.e., viral hepatitis and hepatic fibrosis), use of conventional dose chemotherapy, immunosuppressive agents with azathioprine, and herbal teas with pyrrolizidine alkaloids. The clinical presentation may be asymptomatic, but with increasing SOS disease severity, patients can manifest weight gain, with or without ascites, right upper quadrant pain, jaundice, and renal failure. Onset occurs from 10 up to 30 days after myeloablative therapy is started. A diagnosis of SOS can usually be made on clinical criteria, after ruling out other confounding conditions such as sepsis, drug-induced cholestasis, graft-versus-host disease, or fungal infection. The diagnostic gold standard for SOS is measurement of wedged hepatic vein pressure (HVPG) gradient by transjugular liver biopsy (HVPG > 10 mmHg has positive predictive value of > 85% for the diagnosis of SOS). Diagnostic imaging is not diagnostic by itself, but Doppler ultrasound is recommended to rule out other causes and will often demonstrate hepatomegaly and ascites in support the diagnosis.

The management of established SOS is supportive care, diuretics, abdominal paracentesis, and dialysis as needed. There are no randomized controlled trials to definitively support the Defibrotide.

5. Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) is due to "hepatic venous outflow tract obstruction", independent of the level or mechanism of obstruction. BCS is classified according to the level of obstruction – small hepatic veins, large hepatic veins, or inferior vena cava. BCS is caused by either secondary malignant vein invasion, or due to primary venous thrombosis or phlebitis (often related to underlying myeloproliferative disease or other hypercoagulable risk factors).

The clinical presentation of BCS can varies from asymptomatic to acute liver failure. The classical symptoms include fever, abdominal pain, ascites, lower extremity edema, gastrointestinal bleeding, and hepatic encephalopathy. Jaundice is uncommon. Liver enzymes and liver function tests may be normal or abnormal. Serum ascites-albumin gradient > 11 micromole/L is supportive of BCS.

Doppler ultrasound of the abdomen may help establish the diagnosis of BCS by showing absent flow or reversed/turbulent flow in the large hepatic vein, in association with intrahepatic or subscapular hepatic venous collaterals. A confirmatory CT and MRI study may be needed in

difficult cases, or as an alternative to Doppler ultrasound. A liver biopsy is usually not required; its main yield is to show congestion, liver cell loss and centrilobular fibrosis.

The clinical strategy proposed by expert consensus treatment includes anticoagulation (usually indefinitely in persons with a permanent underlying risk factor for thrombosis), supportive care, management of portal hypertension complications, and treatment of the underlying condition if applicable. The use of stenting or angioplasty is reserved for short segment stenosis. Transjugular portosystemic shunt (TIPS) is recommended for unresponsive patients, liver transplantation is a last resort if TIPS fails, and if there is fulminant liver failure.

6. Hereditary Hemorrhagic Telangiectasia (HHT) (aka OWR [Osler-Weber-Rendu] Syndrome)

HHT is a rare congenital autosomal dominant disease characterized by widespread cutaneous, mucosal and visceral arteriovenous malformations. These AVMs may involve the lung, brain and/or liver. The liver had widespread microscopic and macroscopic vascular malformation, resulting in three types of functional shunts: arteriovenous, portovenous and arterioportal. In 75% of HHT patients, the vascular malformations can be visualized by using sensitive diagnostic imaging techniques. The typical clinical presentation is a female ~age 30, with high output heart failure due to a hyperdynamic circulatory state, portal hypertension and biliary ischemia, all of which can occur simultaneously or successively. Suggestive clinical characteristics include epistaxis, mucosal telangiectasies, as well as family history of stroke or intracerebral hemorrhage (from cerebral arteriovenous malformations). The most common liver enzyme abnormalities include elevations of alkaline phosphatase (AP) and gamma-glutamyl-transpeptidase (GGT); liver function is preserved. In difficult cases, genetic testing can be done for the most common coding sequence mutations. The gold standard for diagnosis of HHT of liver vascular malformations is angiography, but can usually be determined by non-invasive methods such as Doppler ultrasound and CT scan demonstrating heterogeneous enhancement or hypervascularization of the liver and common hepatic artery enlargement. The liver has widespread microscopic and macroscopic vascular malformations, resulting in three types of functional shunts: arteriovenous, portovenous and arterioportal. A liver biopsy is not recommended due to potential risk and frequent problems with histological misinterpretation.

No treatment is necessary for patients who have asymptomatic liver involvement with HHT. The management of symptomatic patients depends on the clinical presentation – i.e., congestive heart failure, portal hypertension complications, or abdominal pain from biliary ischemia. The experimental antiangiogenic drug VEGF (antibody to vascular endothelial growth factor) has shown promising data for symptom relief. Hepatic artery embolization is only considered for patients with intractable heart failure who have failed maximal medical therapy, and who are not candidates for liver transplantation. Liver transplantation is the only definitive curative therapy, and should be considered for acute biliary necrosis syndrome, intractable heart failure, or portal hypertension.

Chapter 23: Neoplasms of the Liver
K. W. Burak

1. Introduction

Neoplasm of the liver can be categorized as cystic or solid, benign or malignant, and primary or metastatic (Figure 1). With the frequent use of abdominal imaging such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI), many benign tumours of the liver are found incidentally. Metastases from cancers of the lung, colon or breast are relatively common and the prognosis is related primarily to the underlying type of cancer. Worldwide, hepatocellular carcinoma (HCC) is a very common malignancy and is most often related to chronic hepatitis B infection. In North America, HCC is on the increase and is most often associated with cirrhosis of the liver related to chronic hepatitis C. The treatment of HCC depends on the stage of the tumour, the performance status of the patient and the underlying liver function. Cholangiocarcinoma (CCA) is a primary cancer arising from the bile ducts, often in response to chronic inflammation, and has a very poor prognosis. This chapter will review the diagnostic features and management of common benign and malignant neoplasms of the liver.
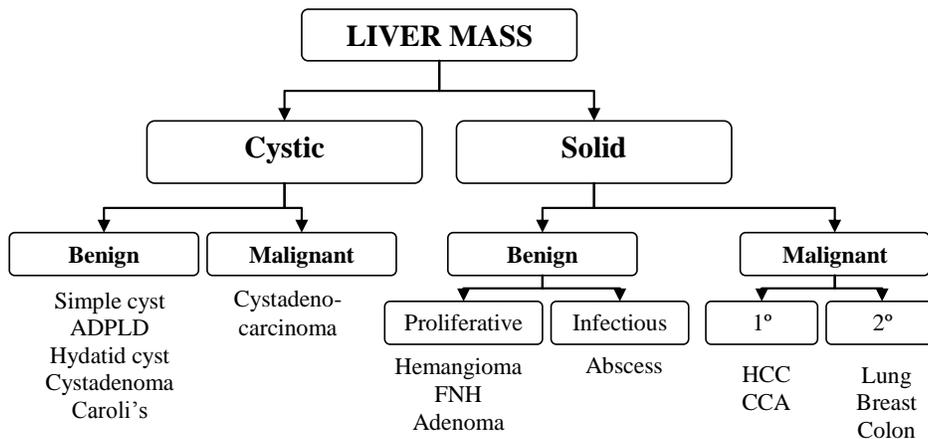
Figure 1. Approach to a Liver Mass.

Abbreviations: 1° = primary, 2° = secondary, ADPLD = autosomal dominant polycystic liver disease, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, CCA = cholangiocarcinoma

2. Benign Tumours of the Liver

2.1. Cystic Neoplasms of the Liver

Hepatic cysts are relatively common, especially in individuals over the age of fifty. Solitary cysts are reported to occur in 3-5% of the population and are four times more common in women. Simple cysts are easily characterized by ultrasound and further imaging is rarely required (Figure 2A). Simple cysts are usually asymptomatic, but rarely, they may present with right upper quadrant (RUQ) pain or fever if complicated by hemorrhage or infection. All other potential explanations for symptoms should be ruled out before pain, bloating or early satiety is

attributed to a hepatic cyst. Treatment is rarely required unless the patient is truly symptomatic. Percutaneous aspiration is associated with a high recurrence rate unless combined with sclerotherapy. Laparoscopic surgical fenestration is usually preferred if the lesions are very large or complicated.

Multiple cysts in the liver may represent autosomal dominant polycystic liver disease (ADPLD) which often coexists with autosomal dominant polycystic kidney disease. The cysts in ADPLD can lead to painful massive hepatomegaly, abdominal distention and early satiety. Selected patients with massive hepatomegaly may have benefit from surgical resection or fenestration but this often only provides temporary relief of symptoms. Liver transplantation, with combined renal transplant if there is coexisting renal failure, is sometimes needed. A randomized placebo controlled trial has demonstrated a benefit long acting octreotide to slow the progression of liver and kidney cysts in these patients.

If a cystic lesion has internal debris, septations or daughter cysts it is considered a complex cyst and it raises the possibility of a cystadenoma or hydatid cyst disease (Figure 2B). Cystadenomas are rare cystic liver tumours which are mucin filled and often have a solid (papillary or stromal) component in the wall. Even if asymptomatic, they should be removed surgically, because rarely these benign tumours may progress to malignant cystadenocarcinoma. Hydatid disease is caused by the zoonotic parasites *Echinococcus granulosus* or *E. multilocularis*. These parasites have part of their life cycle in dogs (definitive host) and sheep (intermediate host). Humans who contact infected animals may become accidental intermediate hosts. The disease is endemic in sheep raising areas in the Middle East, Asia, Africa, South America and Australia. Immigrants from these regions with complex liver cysts should have echinococcal serology ordered. Patients should receive therapy with albendazole before surgical or percutaneous therapy is performed. Cystic fluid can result in intense anaphylactic like reactions if it is released into circulation, but PAIR therapy (Percutaneous Aspiration, Injection of hypertonic saline and Reaspiration) is associated with a low risk of allergic reactions.

Caroli's disease is a congenital abnormality of the biliary system that often presents in childhood. The cystic lesions of the liver represent dilated segments of the bile ducts and communication with the biliary system is best confirmed with MRI and magnetic resonance cholangiography (MRC). Patients may have recurrent bouts of cholangitis and may form intrahepatic biliary stones. The condition can also be associated with congenital hepatic fibrosis, which may lead to liver failure and portal hypertension.

2.2. Pyogenic Liver Abscess

Pyogenic liver abscess (PLA) is most commonly related to biliary obstruction, but can also result from intra-abdominal infections (diverticulitis, appendicitis, inflammatory bowel disease, pelvic sepsis) or from hematogenous spread (endocarditis, dental infections). It has also been reported as a complication of non-operative therapy for primary hepatocellular carcinoma (see below) after transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). Diabetics and immunocompromised hosts appear to be at higher risk for the development of PLA. Patients may present with non-specific symptoms early on in the course of the infection (malaise, arthralgias, anorexia) before the onset of fever and RUQ pain. CT is more accurate than US and enhancement of abscess wall on contrast CT is diagnostic (Figure 2C), especially in a patient with fever and an elevated white blood cell count. Furthermore, a CT may elucidate the source of the PLA in many patients. Blood cultures should be drawn and broad-spectrum

antibiotics should be started to cover both aerobic and anaerobic gram negative and positive bacteria. Typically, antibiotics are delivered intravenously for the first two weeks, followed by at least another 4 weeks of oral antibiotics. Percutaneous aspiration or drainage is performed by US or CT guidance and only rarely is surgical resection required.

Amoebic liver abscess usually occurs several months after returning from travel to endemic areas. The protozoan *Entameba histolytica* can cause diarrhea (amoebic colitis) and liver abscess (usually single, large, and loculated), although the two rarely present at the same time. US has a high diagnostic accuracy and serology can help with the diagnosis. Necrosis within the abscess leads to the typical "anchovy paste" appearance. Treatment is with metronidazole and patients without resolution of symptoms may need to undergo aspiration.

2.3. Hemangioma

Hemangiomas are the most common benign tumor of the liver and are seen in 5-20% of the general population. These vascular lesions are usually asymptomatic and are six times more common in women. Hemangiomas present at all ages but are most commonly seen in the third to fifth decades. Lesions larger than 4 cm are called *giant cavernous hemangiomas*, and rarely they can result in pain (from stretching the liver capsule) or a consumptive coagulopathy (Kasabach-Meritt syndrome) when they are very large. They are hyperechoic on US and doppler studies can confirm filling vessels in the periphery. Contrast enhanced CT and MRI show peripheral nodular enhancement (puddling of contrast) with progressive centripetal filling (Figure 2D). RBC-labeled nuclear medicine scans can be used for diagnosis if other imaging modalities are non-diagnostic. No treatment is need for these lesions as they have no malignant potential and the risk of hemorrhage is extremely rare.

2.4. Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is the second most commonly encountered benign liver lesion, occurring in 3% of the population. It is eight times more likely to occur in women, but its association with the use of the oral contraceptive pill (OCP) is controversial. It is postulated that they form in response to micro-thrombosis of branches of the portal vein, with that area of the liver growing aberrantly because of it predominant arterial blood supply. Histologically, they are hypervascular, often with a central scar, and although they lack of normal venous anatomy they contain all of the normal cells of this liver (including Kuppfer cells). On US they are isoechoic and the central scar may be evident. Contrast enhanced ultrasound (CEUS) can differentiate from adenoma by a centrifugal filling pattern in the arterial phase and stellate vascularity. On CT there is transient arterial phase enhancement with the central scar being more evident on delayed imaging. The central scar can often be seen on MRI (Figure 2E) and the use of MR hepatobiliary specific contrast agents (Gd-EOB-DTPA or Primovist®) is particularly good at differentiation between FNH and adenoma. Technetium sulfur colloid scans will often show normal or increased uptake in the lesion due to the presence of the Kuppfer cells. No therapy is required for FNH as these lesions have no malignant potential and they rarely bleed or cause other symptoms.

2.5. Adenoma

Hepatocellular adenoma is a rare mass lesion of the liver characterized by the benign proliferation of hepatocytes. They are eleven times more common in women and are clearly associated with the use of the OCP. In men they are often the result of anabolic steroid use. Patients can present with multiple adenomas, with hepatic adenomatosis being associated with glycogen storage disease. Many patients are asymptomatic, but up to one quarter of patients may present with pain in the epigastrium. Adenomas can rapidly grow in response to high estrogen states, such as pregnancy or ongoing use of the OCP, and they can present with shock due to a hemoperitoneum following spontaneous rupture. Although benign, it is estimated that approximately 10% of adenomas will undergo a malignant transformation, with the risk being highest for larger adenomas. Adenomas do not have specific findings on US. CT scanning typically demonstrates arterial phase enhancement which becomes isointense on later imaging. Often lesions show intralesional hyper- or hypo-densities related to necrosis or hemorrhage (Figure 2F). MRI may show the presence of microscopic fat within the lesion. Sulfur colloid studies may show the characteristic lack of uptake due to absence of Kuppfer cells in the adenoma. Management includes stopping the OCP and resection of lesions larger than 5cm or symptomatic tumours.
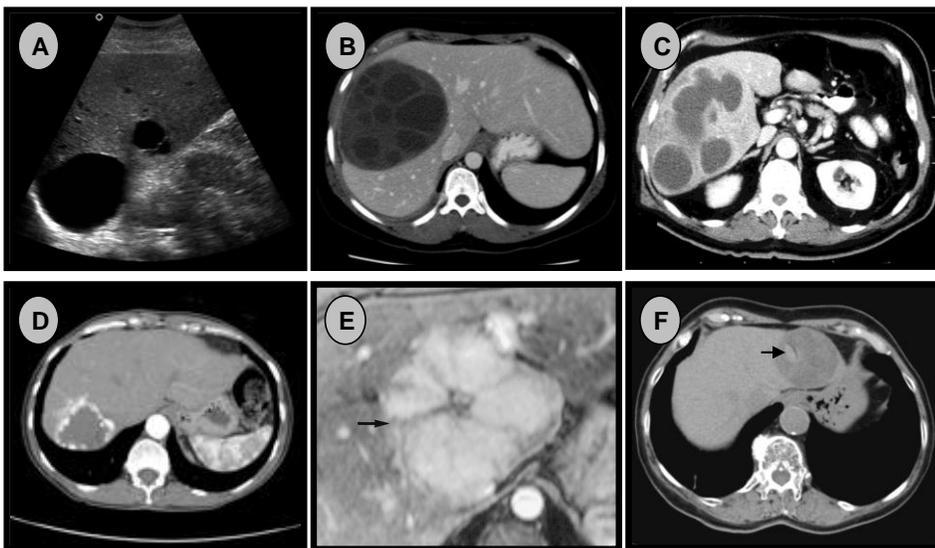
Figure 2. Radiographic findings of benign liver tumours. A) Simple cyst – hypoechoic on US with no internal septations or debris; B) Hydatid cyst – complex cystic mass on CT scan; C) Pyogenic liver abscess – note enhancement of the wall on CT scan; D) Hemangioma – CT scan demonstrates peripheral puddling of contrast; E) Focal Nodular Hyperplasia – MRI demonstrates the classic central scar (black arrow); F) Adenoma – CT scan demonstrates hyperenhancing area of recent hemorrhage (black arrow).

3. Malignant Tumours of the Liver

3.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the third leading cause of cancer related mortality world-wide. Each year there are more than 600,000 new cases, with more than half of them occurring in China alone. Although a rare malignancy in Western countries, HCC is one of only a few cancers with an increasing incidence in North America. Globally, hepatitis B virus (HBV) infection is the leading cause of HCC. In North America, HCC occurs in the setting of cirrhosis in more than 80% of cases, with hepatitis C virus (HCV) being the leading cause. HCC is two to three times more common in men compared to women. Screening for HCC should be performed in all patients with cirrhosis and chronic carriers of HBV (Asian males over the age of 40, Asian females over the age of 50, and Africans over the age of 20). US performed every six months is the recommend screening modality. Alfa-fetoprotein (AFP) is only elevated in approximately 60% of HCC and can be falsely elevated by flares of viral hepatitis. Because it lacks sensitivity and specificity, AFP is no longer recommended as a screening test for HCC, although many clinicians still use US and AFP in combination.
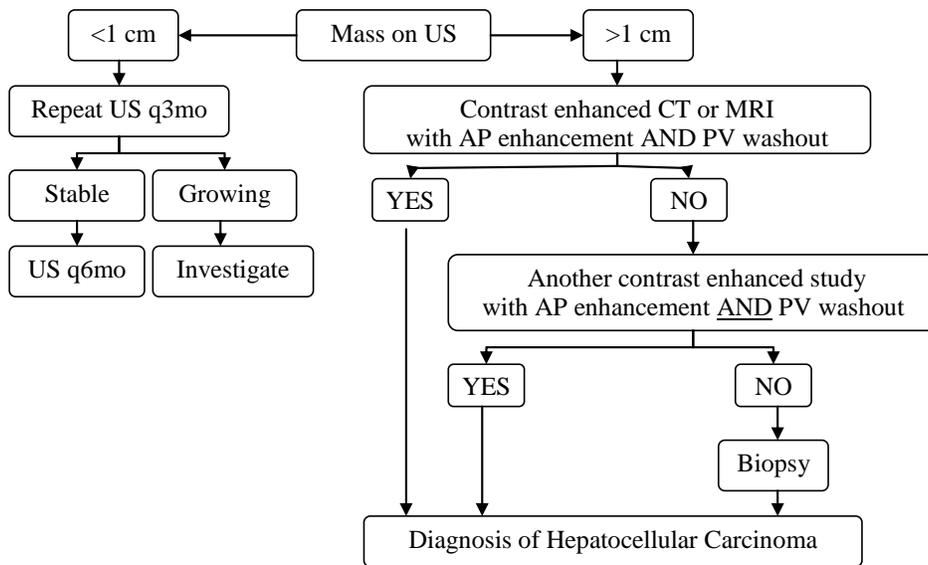
Figure 3. Diagnosis of hepatocellular carcinoma (HCC) in a cirrhotic liver.

Abbreviations: US = ultrasound, AP = arterial phase, PV = portal venous

Adapted from AASLD Practice Guidelines: Bruix J and Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2010. (available on-line at http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20practice%20Guidelines/Hccupdate2010.pdf

To establish the diagnosis of HCC, an elevation of AFP >200 ng/mL is helpful, but contrast enhanced imaging is needed. When a small (<1cm) suspicious nodule is identified on US it should be followed more closely with US every 3 months until it shows stability over time (Figure 3). If it is larger than 1 cm, the nodule should be investigated with a contrast enhanced CT, MRI or US. Because these malignant tumours derive most of their blood supply from the hepatic artery, a HCC will show enhancement in the early arterial phase (Figure 4). In later images, as the remainder of the liver is perfused with contrast arriving from the portal vein, the HCC (which has very little blood supply from the portal vein) will appear darker than the rest of the liver. This pattern is referred to as portal venous "washout" (Figure 4). Arterial phase enhancement and portal venous washout for a lesion > 1 cm in the setting of cirrhosis is highly specific for HCC. Recently, the specificity of CEUS has been questioned as intrahepatic peripheral cholangiocarcinoma (CCA) have been found to have similar vascular patterns to HCC. A biopsy is needed to confirm HCC only when the contrast CT or MRI is not classic and the AFP is <200 ng/mL. Biopsies are now rarely performed to establish the diagnosis of HCC because they are associated with a risk of bleeding, a 1-2% chance of tumour seeding, and biopsies of small lesions can be falsely negative in more than 10%.

| **Unenhanced** | **Arterial** | **Portal Venous** |
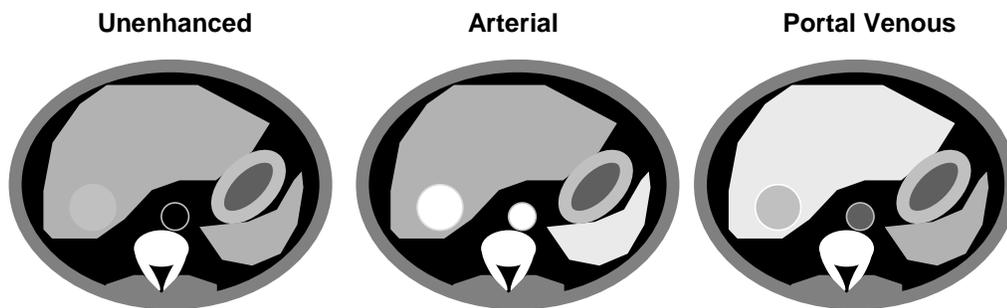
Figure 4. Diagnosis of hepatocellular carcinoma (HCC). The classic HCC, which may be barely perceptible on unenhanced CT or MRI, will be enhancing on the arterial phase and will demonstrate "washout" compared to the rest of the liver on the portal venous phase.

The management of HCC is complex and is best performed in a multi-disciplinary group, consisting of hepatologists, surgeons, oncologists, and interventional radiologists. It is important to understand the competing risks for mortality of the cirrhotic liver and the HCC. The preferred staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, as it takes into account the tumour stage, the liver function according to the Child-Turcotte-Pugh (CTP) system, and the patient performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG). Furthermore, it has the advantage of linking these prognostic factors to recommended therapies. The Alberta HCC algorithm (Figure 5) incorporates local selection practices for the various treatment options of HCC into the BCLC staging system.
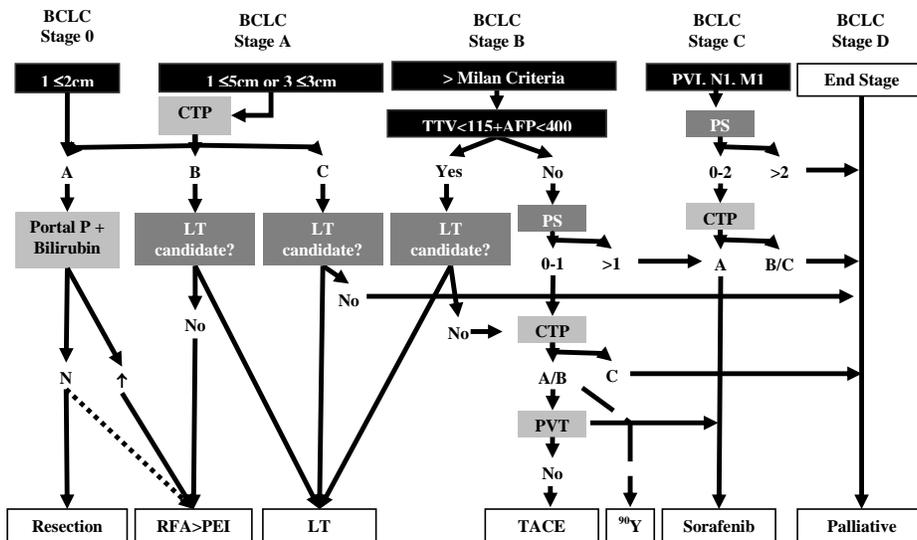
Figure 5. Management of hepatocellular carcinoma according to the Alberta HCC algorithm. The algorithm recognizes the importance of tumour properties (size, number, extra-hepatic spread and AFP) [black boxes], patient characteristics (performance status and candidacy for transplantation) [dark grey boxes], and liver function (CTP class along with elevated pressure within or thrombosis of the portal vein) [light grey boxes] and links patients to most appropriate therapy [white boxes]. Dotted line represents potential role of RFA in very early stage HCC. Dashed line recognizes potential role of ^{90}Y radioembolization, especially for patients who are not candidates for TACE because of bland portal vein thrombosis.

Abbreviations: BCLC= Barcelona Clinic Liver Cancer; PVI = portal vein invasion; N = lymph node; M = metastases; CTP = Child-Turcotte-Pugh class; TTV = total tumour volume; AFP = alpha-fetoprotein; PS = performance status; Portal P = portal pressure; LT = liver transplantation; PVT = portal vein thrombosis; RFA = radiofrequency ablation; PEI = percutaneous ethanol injection; TACE = transarterial chemoembolization; ^{90}Y = transarterial radioembolization with ^{90}yttrium.

Adapted from: Burak KW and Kneteman NM. An Evidence-Based Multidisciplinary Approach to the Management of Hepatocellular Carcinoma (HCC): The Alberta HCC Algorithm. *Can J Gastroenterol* 2010, in press.

In North America, approximately 30% of patients have their HCC detected at an early stage where curative treatment options are possible. Patients with a small single tumour (<2cm) with good PS and well compensated cirrhosis are candidates for surgical resection (BCLC stage 0); however, recent studies have suggested similar outcomes in this patient population with radiofrequency ablation (RFA). BCLC stage A patients may be offered surgical resection, liver transplantation (LT) or RFA depending on their liver function. In carefully selected patients 5 year survival rates of 70% have been reported with all three modalities. Surgical resection should

be reserved for patients with CTP class A cirrhosis, who have a normal bilirubin and no evidence of portal hypertension (no splenomegaly, no varices, platelet count > 100) to avoid post-operative liver failure. Unfortunately, 70% of patients will have a recurrence of HCC in the remnant cirrhotic liver within 5 years of resection. Patients who are not candidates for resection should be considered for LT, as it treats both the liver failure and the liver cancer. The size of the tumour predicts microvascular invasion and subsequent risk of tumour recurrence after LT. The risk of recurrence after LT is low (<15%) if the Milan criteria (single tumour <5cm or 3 tumours each <3cm) are used to select patients. Unfortunately, long waiting times for cadaveric organs means many patients progressing beyond these criteria while awaiting LT. Many centers, including the University of Alberta in Edmonton, have tried to expand the criteria for LT beyond the Milan criteria. Currently in Alberta patients are candidates for LT if their total tumour volume (TTV, measured by $4/3\prod radius^3$) is less than $115cm^3$ and their AFP is <400ng/mL, as these cutoffs result in low recurrence rates and acceptable post-LT survival. This TTV equates to a single tumour ≤6cm or many smaller tumours. If patients are not a candidate for LT they may be treated with RFA. Percutaneous RFA burns the tumour under US guidance and is associated with low complications (2% risk of bleeding, hyperbilirubinemia, damage to adjacent structures) but recurrence rates that are higher than after surgical resection, especially if the tumour is larger than 2cm. RFA has been shown to be superior to percutaneous ethanol ablation (PEI), although PEI may be used for tumours adjacent to large blood vessels where a "heat sink" effect can reduce the efficacy of RFA.

Approximately 50% of patients in North America will present with intermediate or advanced stages of HCC. Patients with large single tumours or multifocal disease, who are not candidates for curative options, can be offered transarterial chemoembolization (TACE) for palliation. TACE takes advantage of the arterialized blood supply of HCC to deliver chemotherapy and embolic particles to the tumour via the hepatic artery. Meta-analysis of randomized trials have demonstrated a survival benefit of TACE in patients with intermediate stage HCC who have preserved liver function (CTP class A or early class B cirrhosis) and good PS. With TACE median survival increases from approximately 16 months to 20 months in BCLC stage B patients. TACE is generally well tolerated but frequently causes post-embolization syndrome (fever, RUQ pain, nausea) and can result in liver failure, especially in patients with portal vein thrombosis (PVT). Transarterial radioembolization (TARE) is similar to TACE but supplies beta-emitting internal radiation with ^{90}yttrium (^{90}Y) microspheres. It has not been compared to TACE in randomized trials, although cohort studies suggest similar outcomes. TARE has the advantage of being performed as an outpatient and can be safely performed in patients with PVT. Advanced stage HCC (BCLC stage C) is characterized by malignant portal vein invasion (PVI) or extrahepatic spread into lymph nodes (N1) or distant organs such as the bone, lung or brain (M1). Sorafenib, a multikinase inhibitor which also blocks vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF), has been shown in a placebo controlled trial to improve survival from approximately 8 months to 11 months. The therapy has only been carefully studied in patients with reasonable PS and well preserved CTP class A cirrhosis. It costs approximately $5,000 per month, and although generally well tolerated, it may result in hypertension, diarrhea and hand-and-foot reactions. Sorafenib is now also being studied as adjuvant therapy to prevent recurrence following curative intent surgical resection or RFA and in combination with TACE in intermediate stage patients. Many other multikinase inhibitors, anti-VGEF drugs and inhibitors of m-TOR (eg. sirolimus and everolimus) are currently being studied in clinical trials. Patients with CTP class C cirrhosis, and those will PS

≥2 (more than half of time confined to bed), who are not LT candidates, should be offered only best supportive palliative care as their prognosis is very guarded (median survival ~ 3 months in BCLC stage D patients).

3.2. Hepatoblastoma

Primary liver tumours account for only about 1% of all childhood malignancies. Hepatoblastoma is a rare malignant tumor that develops in the liver of young children. It accounts for two-thirds of all malignant liver tumours in children (others include HCC, sarcoma, and germ cell tumours). Approximately one-third of patients will present at an early stage where surgical resection can be performed. In other patients, neoadjuvant chemotherapy with cisplatin, 5-fluorouracil and vincristine can be followed by liver transplantation. The five-year survival rate is less than 35% but improves to approximately 70% in patients undergoing transplantation.

3.3. Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a primary liver cancer arising from the biliary epithelial cell. CCA can present in the distal bile duct or hilum (Klatskin tumours) and these patients will often present with painless jaundice. Intrahepatic cholangiocarcinoma (ICC) arises within the liver and may present as an asymptomatic mass lesion without jaundice. ICC is the second most common primary liver cancer and accounts for 10-15% primary liver malignancies. As with HCC, the incidence of ICC is on the increase in North America. ICC is slightly more common in women and the risk increases in the elderly. Risk factors for ICC include chronic inflammation of the biliary system (primary sclerosing cholangitis, choledochal cyst, Caroli's disease, or parasitic biliary infections with *Clonorchis sinensis* or *Opisthorchis viverrini*) or cirrhosis of the liver (HBV, HCV, PBC, NAFLD, etc). Biopsy will reveal adenocarcinoma; however, this pathology within the liver will usually be metastatic (see below) and therefore a workup to rule out another primary malignancy is necessary. CT scan should be performed of the chest, abdomen and pelvis and positron emission tomography (PET) scanning may be helpful to evaluate the extent of disease. The tumour marker carbohydrate antigen 19-9 (CA19-9) has a reasonable sensitivity and specificity for CCA if the level is above 100 U/mL. Surgical resection is the only curative option for ICC but the prognosis remains guarded (5 year survival rates of 15-40%). For patients with unresectable ICC the median survival is approximately 6 months, but the combination of gemcitabine and cisplatin chemotherapy may improve survival.

3.4. Metastatic Tumors

In North America, metastases from another malignancy are the most common malignant tumor to affect the liver. Common sources include lung, breast, colorectal, gastric, pancreatic, urogenital or neuroendocrine tumors. Patients may present with vague symptoms of weight loss, anorexia, low grade fever or symptoms related to the primary malignancy (change in bowel habit, gastrointestinal bleeding, cough or hemoptysis). Metastases are more likely to be multiple small lesions, and on CT they are often described as target ring-enhancing lesions. CT or MRI of the abdomen may also help identify a primary malignancy in the pancreas, colon or urogenital system. The diagnosis is usually confirmed by needle biopsy, and immunohistochemical staining may help identify the likely primary malignancy. A work-up for an unknown primary malignancy should include tumour markers like carcinoembryonic antigen (CEA), which is elevated in colorectal cancer, as well as AFP and CA-19-9 (to exclude primary liver cancers). Women should undergo breast and pelvic exams, as well as mammography and pelvic

ultrasounds. Chest X-ray or CT scan is especially important for smokers. Endoscopy and colonoscopy should be performed to rule out gastrointestinal malignancy.

For most cases, metastatic disease implies an advanced stage of cancer with a poor prognosis. However, patients with metastatic colorectal cancer (CRC) and neuroendocrine tumors may have many therapeutic options and overall these groups may have a reasonable prognosis. Nearly one-half of patients with CRC will develop a liver metastasis. The combination of chemotherapy and surgical resection can significantly prolong survival and quality of life in these patients, with 5 year survival rates of 70% being reported for patients with solitary liver metastases from CRC. Between 50-90% of neuroendocrine tumours will involve the liver. Non-operative treatment options include radioactive labeled therapy with ^{131}I-metaiodobenzylguanidine or ^{111}In-octreotide and chemotherapy. However, prolonged survival and improved quality of life can be achieved in many patients with neuroendocrine liver metastases following resection, RFA, TACE, TARE and liver transplantation.

474
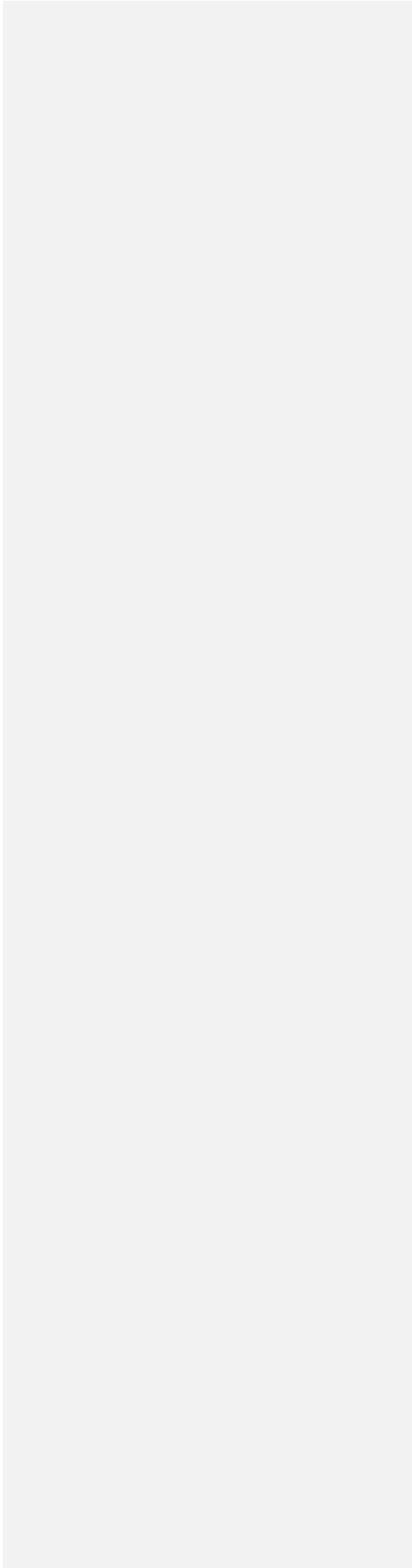
Chapter 24: Congenital Hyperbilirubinemias
P. Paré

1. Introduction

The importance of recognizing congenital hyperbilirubinemia lies mainly in distinguishing it from other, more serious hepatobiliary diseases. Except for Crigler-Najjar syndrome, congenital hyperbilirubinemias do not impair either the quality of life or the life expectancy of affected subjects. Persons with congenital (recessive) hyperbilirubinemia have normal standard liver tests (except of course for elevated serum bilirubin concentrations). The liver histology is also normal, (except for the black pigment accumulation in centrolobular hepatocytes Dubin-Johnson syndrome). With the exception of Gilbert's syndrome, these syndromes are distinctly uncommon and are divided into two groups on the basis of the type of the serum hyperbilirubinemia (Table 1).

Practice points:
o Unconjugated hyperbilirubinemia in absence of hemolysis, is usually secondary to congenital defect in glucuronidation of bilirubin.
o Congenital hyperbilirubinemia does not impact on life expectancy or quality of life of affected individuals, except for Crigler-Najjar type I syndrome, in which patient may require a liver transplantation.

2. Unconjugated Hyperbilirubinemia

2.1. Gilbert's Syndrome

Gilbert's syndrome is the most common congenital hyperbilirubinemia syndrome. Its pathogenesis is related to a partial deficiency in hepatic uridinediphosphoglucuronate glucuronosyltransferase (UGT) enzyme. It is due to a mutation in the promoter region of the UGT1A gene, upstream to exon 1 of the gene encoding bilirubin-UGT. Approximately 9% of the general population in Western countries are homozygous for the variant promoter, and 30% are heterozygous. Other factors are probably involved in the clinical expression of the Gilbert's phenotype since not all homozygous carriers develop hyperbilitubinemia. The syndrome manifests itself only in homozygous individuals; its inheritance is therefore consistent with an autosomal recessive trait. Gilbert's syndrome is usually detected in adolescents and young adults, most commonly in males. Clinically, it does not cause symptoms, scleral icterus may be present slight, and fluctuating, and the physical examination is otherwise normal. Liver tests and hemogram (to exclude hemolysis) are normal except for unconjugated serum bilirubin which is elevated between 20 and 100 μMol/L.

Certain conditions can increase the plasma bilirubin concentrations to higher values (usually less than 200 μMol/L): hemolysis, fasting, a normocaloric diet without lipids, intercurrent febrile illnesses, stress, physical exertion. Hepatic enzyme inducers such as phenobarbital and clofibrate can normalize plasma bilirubin concentrations within a few weeks.

The long-term outcome of subjects with Gilbert's syndrome is similar to that of the general population. In neonates, it may be associated with increased duration or severity of normal post-partum physiological jaundice. Diagnostic tests are usually not necessary but genetic testing is available in certain laboratories. The most important aspect is to recognize the syndrome distinguishing it from other causes of elevated unconjugated hyperbilirubinemia.

Table 1. Congenital syndromes of hyperbilirubinemia

	Unconjugated Hyperbilirubinemia			Conjugated Hyperbilirubinemia	
	Gilbert's	Crigler-Najjar type 1	Crigler-Najjar type 2	Dubin-Johnson	Rotor's
➤ Prevalence	7% of population	Very rare	Uncommon	Uncommon	Rare
➤ Inheritance (all autosomal)	Recessive	Recessive	Recessive	Recessive	Recessive
➤ Serum bilirubin concentration (μmol/L)	< 100 (all unconjugated)	> 400 (all unconjugated)	< 400 (all unconjugated)	< 100 (about half conjugated)	< 100 (about half conjugated)
➤ Genetic basis	Defect in promoter region of UE TIAI gone, reduced UGT enzyme activity	Alterations in UGTAI gene & absent UGT enzyme activity	Point mutations in UGTAI gene→ reduced UGT enzyme activity	Mutations in MRP2 gene→ reduced excretion of organic anions (except blue acids)	Genetic basis unknown
➤ Diagnostic features	Unconjugated Bilirubin concentration: ↑ with fasting, ↓ with phenobarbital	Unconjugated bilirubin: No response to phenobarbital	Unconjugated Bilirubin concentration: ↓ with phenobarbital	Urinary coproporphyrin excretion (isomer 1>80%) - Pigment in centro-lobular hepatocytes - Oral cholecystogram shows delayed or absent	Urinary Coproporphyrin excretion of isomer 1<80%s
➤ Prognosis	Normal	Early death from kernicterus	Usually normal	Normal Excretion	Normal
➤ Treatment	None needed	Liver graft	Phenobarbital	Avoid estrogen	None available

2.2. Crigler-Najjar Syndrome

The Crigler-Najjar syndrome is a rare autosomal recessive disorder. It may present in two types. The phenotypes of the syndromes are caused by a variety of alterations in the coding sequences of the UGT1A1 gene, in contrast to Gilbert's syndrome in which the defect is in the promoter region rather than in the gene itself. In type I, a variety of mutations leads to absent UGT enzyme activity. In type II, genetic lesions consist of point mutations resulting in the substitution of a single amino acid, leading to markedly reduced enzyme activity.

Type 1 is a serious disease characterized by unconjugated hyperbilirubinemia often greater than 400-500 μMol/L. Jaundice occurs almost immediately after birth and may lead to kernicterus with consequent neurologic damage and mental retardation. Kernicterus involves damage to the basal ganglia and cerebral cortex because unconjugated bilirubin is able to penetrate the immature blood-brain barrier of infants. Untreated, death occurs early. Nowadays, most patients treated with phototherapy and plasmapheresis survive postpuberty without significant brain damage. Subsequently, due to thickening of the skin making phototherapy less effective, patients succumb to kernicterus later in life. Liver transplantation is the only curative treatment. Gene therapy may eventually improve the outcome.

Type 2 syndrome is a much more benign condition in which unconjugated hyperbilirubinemia usually does not exceed 400 μmol/L. Patients are much less likely to develop neurologic consequences. Specific therapy may not be necessary. If necessary, phenobarbital or clofibrate reduces bilirubin levels by at least 25% and may improve quality of life of some individuals. Prognosis is good, despite a lifelong persistent unconjugated hyperbilirubinemia.

An important research agenda explore gene therapy for Criggler -Najjar type I syndrome.

3. Conjugated Hyperbilirubinemia

Two conditions characterized by congenital conjugated hyperbilirubinemia without cholestasis have been described, Dubin-Johnson and Rotor syndrome are inherited as autosomal recessive traits. Both are uncommon, believed to result from specific defects in the hepatobiliary excretion of bilirubin. These conditions are benign, and their accurate diagnosis provides reassurance to the patient. Plasma bilirubin levels are usually in the range of 35-85 μmol/L. Plasma bilirubin may increase further in both conditions during intercurrent infection, pregnancy or use of oral contraceptives. Pruritus is absent and serum bile acid levels are normal, as are routine liver tests, except for the serum bilirubin concentration. Bilirubinuria is usually present. No treatment is necessary.

Diagnosis is made by documenting conjugated hyperbilirubinemia (where at least 50% of the total bilirubin is the direct fraction) while other liver tests are normal. Distinction of the two syndromes is made by the characteristic urinary coproporphyrin excretion (D-J, isomer 1>80%; Rotor, isomer 1<80%).

Some distinctive features allow differential diagnosis between the two syndromes.

3.1. Dubin-Johnson Syndrome

The syndrome results from mutations in the MRP2 gene. Biliary excretion of organic anions, except bile acids, is impaired. Patients have a black liver, which results from the accumulation of a melanin-like pigment in lysosomes. Visualization of the gallbladder during oral cholecystography is usually delayed or absent. Urinary excretion of total coproporphyrin is normal, whereas the proportion of isomer 1 is higher than in normal controls (>80%).

3.2. Rotor's Syndrome

       The genetic basis of Rotor's syndrome has not been identified. It is a disorder of hepatic storage. The appearance and histology of the liver are normal. Oral cholecystography usually visualizes the gallbladder. Total coproprophyrin excretion is greater than normal, as in other hepatobiliary disorders, and isomer 1 makes a smaller proportion (<80%) than in Dubin-Johnson patients.
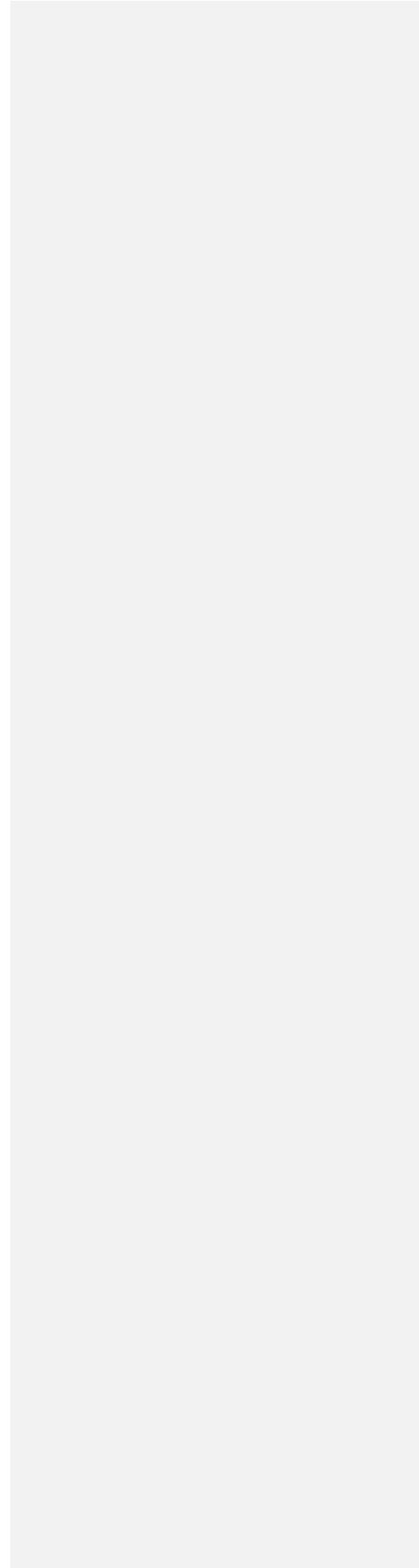
Chapter 25: Drug-Induced Liver Injury

M. Gupta and A. B. R. Thomson

1. Background

Drugs are the second most common cause of acute liver failure, and are the predominant cause of liver injury in the Western world. Drugs account for about 25% of persons admitted for acute hepatitis, and about 50% of persons admitted with acute liver failure (ALF). However, fewer than 10% of drug induced liver injury (DILI) progress to ALF. Incidence has been esitamted to be 1-2/million. However, 80% who develop ALF need transplantation or might die. Adverse events (AEs) can either occur secondary to escalation of drug dosing, or be an idiosyncratic reaction. Rarely do these patients have a background history of liver disease (Andrade et al., Gastro 2005; 129:512-21). The risk of an adverse event (AEs) to a drug is quoted as AEs per number of persons exposed. For example, the risk of hepatic toxicity from NSAIDs is approximately $5/10^5$ persons exposed, $1/10^5$ for amoxicillin-clavulinic acid. Drug-induced liver injury (DILI) is under recognized because the diagnosis is often based in the exclusion of other conditions. It has been estimated that the incidence of DILI is approximately 10 cases per 100,000 patient years.

When the serum ALT (Alanine Aminotransferase), AP (Alkaline Phosphatase) or bili' (bilirubin) rise to two-times the upper limit of normal or higher, it is prudent to explore the possibility of liver disease caused by drugs. If a medication is having a toxic effect on the liver, it should be stopped quickly in the hope that the liver damage will not progress. However, despite that, many cases follow a sub-acute course with progression to liver failure. This is important, because the mortality rate for the persons hospitalized for DILI (adverse hepatic drug reactions associate with an abnormal liver biopsy) is 10%, largely related to acute liver failure (such as from acetaminophen). According to the Zimmerman "Hej's rule", ALT > 8x ULN, or ALT plus bilirubin increases suggest the 10% potential for acute liver failure. Use of a web-based search for drug effects in a patients dossier will show that most drugs can result in abnormal liver enzymes tests (LEs) or liver function tests (LFTs). Hence, virtually any drug, toxin or herbal preparation may damage the liver. At least 300 agents have been targeted.

The Acute Liver Failure Study Group from 23 US academic centres reported 1400 cases of acute liver failure (ALF) over the decade ending in 2008 (Stravitz and Kramer, 2009). Excluding the cases of acetaminophen (45%) overdose, 15% of cases were idiosyncratic reactions to drugs (e.g. NSAIDs, anti-convulsants, antibiotics). Marked elevations in transaminases reflect an hepatocellular pattern in 87% of patients, while 13% had a cholestatic pattern. Hepatocellular variety has been documented to carry worse prognosis, compared to cholestatic. It is important to note that the drug-associated ALF patients are often found to have consumed the offending drug for a median of three months. So it is important to obtain an extensive list of all medications including OTC (over-the-counter), prescription drugs and herbal preparations taken in the past several months. There was a wide range of offending drugs (Table 1).

The outcome of persons with drug-induced ALF is poor: without a liver transplantation, about one third died (Table 2).

Other drugs:
Propylthiouracil (19)
Disulfiram (9)
Halothane (8)
Herbal (6)
Amitriptyline (2)
Nefazodone (2)
Methotrexate (5)
Troglitazone (4)
Methyldopa (5)
Mercaptopurine or azathioprine (3)
Fialuridine (3)
Single cases*

Antituberculosis:
Isoniazid (48)
Isoniazid plus another
anti-tuberculosis drug (2)

Anti-epileptics:
Phenytoin (20)
Valproate (20)
Carbamazepine (3)
Single case:
Felbamate

Non-steroidal anti-inflammatories:
Diclofenac (3)
Bromfenac (2)
Ibuprofen (2)
Single cases:
Etodolac
Naproxen
Indometacin

Statins:
Atorvastatin (3)
Cerivastatin (2)
Simvastatin (2)
Single cases:
Pravastatin
Ezetimibe
Fluvastatin

Antibiotics:
Nitrofurantoin (12)
Ketoconazole (8)
Amoxicillin and clavulanate (5)
Trimethoprim-sulfamethoxazole (2)
Minocycline (2)
Single cases:
Terbinafine
Ciprofloxacin
Telithromycin
Levofloxacin
Itraconazole
Moxifloxacin

Figure 1. Non-paracetamol-based drugs causing acute liver failure in patients requiring emergency liver transplantation in USA, 1987-2006

Permission granted: Bernal et al., *Lancet* 2010; 376:190-201.

Table 1. Drugs other than acetaminophen implicated in causing acute liver failure

- Antibiotics
  - Isoniazid alone, or in combination with other antituberculosis drugs
  - Nitrofurantoin

- MSK
  - NSAIDs

- Metabolic
  - Statins
  - Propylthiouracil

- Anti-seizure
  - Phenytoin

- Micellaneous
  - Complementary or alternative medications, or illicit "street" drugs

Source: Reuben A, et al. Drug-induced acute liver failure: Results of U.S. multicentre, prospective study. Hepatology 2010,52:2065.

Table 2. Outcome of non-acetaminophen-associated cases of acute liver failure (ALF)

o Liver transplantation	42%
o Died while waiting liver transplantation	13%
o Not suitable for liver transplantation and died	18%
o Spontaneous recovery	27%

It is important to remember medications used to treat various complex medical diseases may be associated with liver damage. Thus, assuming that the abnormal liver enzyme abnormality is due to the underlying disorder for which the medications are being used is not always sufficient to explain the extent of abnormal LEs (Table 3).

Table 3. Drug associations with other diseases, and genetic determinants

- Drug Associations with other diseases

o ASA (salicylates)	- Rheumatoid arthritis in adults
o Methotrexate (hepatic fribrosis	- Accentuated by ALD and NAFLD, diabetes, obesity, chronic renal disease
o Tetracycline (fatty liver)	- Renal disease
o Anti-cancer drugs (sinusoidal Obstruction Syndrome)	- Bone marrow transplant, HCV
o Sulfonamide	- HIV/AIDS
o Azathioprine (vascular disease)	- Renal transplantation patients

- ➢ Genetic determinants
  - o Penicillin
  - o Valproic acid (inherited mitochondrial diseases)
  - o Amoxicillin-clavulinic acid (HLA halotype associates)

Table 4. Treatment for GI disorders commonly associated with Hepatotoxicity

➢ Esophagus	o H$_2$-RAs, PPIs o Beta-blockers o Calcium Chanel Blocker	- gastrointestinal reflux disease - portal hypertension esophageal - - - dysmotility syndromes
➢ Stomach	o H$_2$-RAs, PPIs o ASA, NSAIDs, COXIBs	- peptic ulcer disease, dyspepsia, - gastroprotection - gastric damage (ulcers, upper GI bleeding; gastric or duodenum), perforation
➢ Small bowel	o Azathioprine, methotrexate, Salazopyrine/mesalamine	- inflammatory bowel diseases
➢ Liver	o HAART, alcohol	- HIV/AIDS

---

2. Risk Factors

The risk of drug AEs depends on the drug in question, and is influenced by genetic factors; age (<60 yr); gender; dose; duration of alcohol use; obesity; current nutritional status; family history; previous liver disease; previous drug reactions.

There are three inducible/adaptable hepatic pathways of drug metabolism:

I – Alter the parent drug molecule by oxidation, reduction, or cytochrome P450 enzymes via more than 20 hydrolytic reactions

II– Conjugation with sugar, amino acid or sulphate to increase water solubility, and therefore excretion of drug (e.g. glucuronyl transferase).

III-Energy dependant carrier-mediated excretion of drug, its metabolite or conjugate into bile by ATP-binding cassette (ABC) proteins such as MDR$_1$ (multidrug resistance protein 1) and MRP's (multidrug resistance-associated proteins)

Presence of deep jaundice, raised ALT/AST and increasing age are associated with a higher mortality (Bjornsson et al., Hepatology 2005; 42:481-9). There are numerous mechanisms of liver injury, but it is not always possible to determine which mechanism of injury is responsible for the hepatotoxicity (Table 5).

Drug-associated liver injury may have no known explanation ("idiosyncratic") mitochondrial damage leading to features including microvascular fatty liver and inhibition of hepatic mitochondrial DNA replication. DILI may cause cholestasis resulting from impairment of the hepatobiliary system for bilirubin or bile acid uptake, as a result of the offencing drug binding to transporters (eg, systems for bilirubin or bile acid uptake, as a result of the offencing

drug binding to transporters (eg, BSEP [ABC B11], MDR1 [ABCB1], MRP2 [ABCC2] and MDR3 [ABCB4]). Finally, drugs or drug metabolites may act as haptens and bind covalently to hepatic proteins. These drug-protein adducts may lead to an immune response involving CD4^{+}, CD8^{+} t-cells, and Fas ligand mediated hepatocyte apoptosis.

Table 5. Mechanism of liver injury by drug and toxins

o Direct damage to hepatic membranes and mitrochondria
o ROS (reactive oxygen species) overwhelming hepatic antioxidant systems such as the glutathione system, activating signally by Fos, JNK (impaired assembly of microtubules and abnormal folding of protein, p53)
o Oxidation of proteins, fatty acyl groups of phospholipids (lipid peroxidation) and nucleosides
o Post-translational changes in proteins through ADP ribosylation or protease activation, activation of endogenous endonucleases and cleavage of DNA, activation of phopholipases leading to membrane damage
o Activation of hepatic stellate cells and Kupffer cells, as well as damage to endothelial cells
o Immunopathogenic mechanism such as formation of neoantigens (haptens) or drug-protein adducts, or drug-induced autoimmunity leading to drug-induced antibodies
o Hepatic drug reactions may be dose-dependent or idiosyncratic due to metabolic idiosyncracy or immune allergy

Just as there are several mechanisms responsible for liver injury, different hepatic cell sited may be involved, giving the rise to a range of clinical presentations.

Table 6. Drug induced hepatic injury may affect several different cellular sites and give rise to various presentations

Cellular Site	Type of Hepatic Injury
o Hepatocyte	- Hepatitis: acute, chronic, granulomatous
o Bile duct	- Cholestasis: with or without associated hepatitis or bile duct injury
	- Cholangitis: with or without cholestasis, vanishing bile ducts, or sclerosis
o Fat cells	- Steatohepatitis
	- Acute steatosis
o Sinusoidal cells	- Sinusoidal obstruction syndrome
	- Nodular regeneration hyperplasm
o Tumors	- Adenoma, HCC, angiosarcoma

3. Clinical Presentation

There are a variety of presentations for the persons with drug associated hepatotoxicity, ranging from the finding of abnormal liver enzyme tests in the asymptomatic persons, to life-

threatening, systemic acute liver failure (Figure 1, Table 7). A recent NIH workshop has provided a framework for making the diagnosis of DILI.

Table 7. Clinical features of acute liver failure

- Whole body
  - Systemic inflammatory response
  - High energy expenditure and catabolism

- Liver
  - Loss of metabolic function
  - Decreased gluconeogenesis leading to hypoglycemia
  - Decreased lactate clearance leading to lactic acidosis
  - Decrease ammonia clearance leading to hyperammonemia
  - Decreased synthetic capacity leading to coagulopathy

- Lungs
  - Acute lung injury
  - Adult respiratory distress syndrome

- Adrenal gland
  - Inadequate glucocorticoid production contributing to hypotension

- Bone marrow
  - Frequent suppression, especially in viral and seronegative disease

- Circulating leukocytes
  - Impaired function and immunoparesis contributing to high risk of sepsis

- Brain
  - Hepatic encephalopathy
  - Cerebral edema
  - Intracranial hypertension

- Heart
  - High output state
  - Frequent subclinical myocardial injury

- Pancreatitis
  - Particularly in paracetamol-related acute liver failure

- Kidney
  - Frequent dysfunction or failure

- Portal hypertension

    o   Might be prominent in subacute disease and confused with chronic liver disease

---

Permission to reprint: Bernal et al., *Lancet* 2010; 376:190-201

Table 8. From asymptomaic to life threatening presentations

    o   Suspicion: Drug, rash, eosinophilia, organ involvement

    o   Reactive metabolite syndrome (RMS) – idiosyncratic drug reactions in any organ system

    o   Associated Risk factors

RMS in 1st degree relative	1 in 4
Use of steroids, valproic acid	5-X ↑
Lupus	10-X ↑
HIV/AIDS	100X ↑

    o   Acute liver failure

---

4. Example of Drugs

4.1. Acetaminophen

Acetaminophen is an effective over-the-counter analgesic, and is safe when taken in a daily dose that does not exceed 4 gm. It is an example of dose-dependant hepatotoxicity. It is the # 1 cause of ALF in the USA, UK and Western Europe. There are many risks which modify the risk of hepatotoxicity. For example the malnourished, alcoholic taking an acute dose of acetaminophen of >100mg/kg or a 10 to 20 gm dose over three days will develop: acute zone 3 necrosis, extending to bridging or panacinar (massive) necrosis. Liver failure may result from attempted suicide or therapeutic misadventure, as confirmed by a recent literature review (Larson et al., 2005). Remember the rule of "20s". Fatal cases usually involve 20 gm acetaminophen (caution in the heavy alcohol abuser, where even 2 gm may be fatal). Over 20% develop severe liver injury, and of these, 20% die from the hepatotoxicity.

There are two mechanisms of DILI for acetaminophen. The metabolism involves the formation of the highly reactive intermediate metabolite, NAPQ1 (N-acetyl-p-benzo quinine imine). At therapeutic doses, only a small amount of acetaminophen is initially metabolized by the phase I reactions of cytochrome P450 (CYP) –mediated oxidation, followed by phase II conjugation reactions. What acetaminophen which is oxidized by the CYP2E1 and CYP3A4 isozymes produces only a small amount of NAPQ1, which is readily detoxified by binding of the small amounts of NAPQ1. In contrast, when high doses (generally > 4 gm/day) of acetaminophen are ingested, the sulfation and glucuronidation pathways are overcome, the NAPQ1 is not detoxified, the liver stores of glutathione are depleted, and the excess NAPQ1, damages the liver by binding to intracellular proteins, preventing the normal function of the nuclei and mitochondria. This in turn leads to the production of reactive oxygen species, hepatocellular apoptosis, and centrilobular necrosis. If the necrosis is sufficient, the person develops acute liver failure.

The second mechanism of acetaminophen toxicity relates to possible genetic polymorphism in the genes which encodes the enzyme such as glutathione S-transferase as well as those of the CYP family, leading to the recognized variability of person's susceptibility to

develop DILI. Also, results of studies in animal models and humans suggest a role for variation in the expression of CD44 in acetaminophen hepatotoxicity.

Hyperacute injury to the liver occurs within 48 to 72 hours after acetaminophen ingestion. Characteristically, ALT and AST levels rise > 1000 u/L (often 2000 to 10,000 u/L) with associated low bilirubin. There may be nausea, vomiting, fever , malaise, pain (acute dilation of liver with stretching of pain-sensitive liver capsule membrane), with associated symptoms/signs of liver failure [such as jaundice, coagulopathy, renal failure hepatorenal syndrome or acute tubular necrosis (ATN), and hepatic encephalopathy]. Death can occur in 4 to 8 days from cerebral edema, sepsis, liver and multi-organ failure.

After 4 hours of taking an overdose, when most of the acetaminophen has been emptied from the stomach and absorbed, blood levels reflect the prognosis. The risk is assessed with the Prescott nomogram, which plots the plasma concentration of acetaminophen versus hours post-ingestion. Note that with chronic intake, blood levels of acetaminophen are not a reliable indicator of liver injury as it is with acute overdose. The use of cysteine (thiol) donors orally or IV NAC (N-acetyl cysteine) (e.g. oral dose: 140 mg/kg loading dose, then 70 mg/kg every 4 hours for 72 hours) should be administered as late as 36 h after self poisoning as it may be beneficial. If the patient cannot retain orally administered NAC, then the thiol donor may be given intravenously, although the risk of adverse events (rash, angioedema, shock and death) is slightly higher compared to oral route.

From an understanding of the metabolism of acetaminophen we can appreciate the reason for the lag interval, variable dose dependency, effects of alcohol, drugs, fasting, and malnutrition, and the potential therapeutic benefit of a cysteine donor. With acute doses of acetaminophen (> 10 g/day), and during the first 48 hours after overdose the primary pathway is overwhelmed and the secondary pathway becomes involved (Figure 2). The oxidative metabolism of acetaminophen to $NAPQ_1$ and subsequent oxidation of thiol injures mitochondrial function and activates pathways for all cells by the induced cytochrome P450 system (CYP 2E1 or CYP 3A4), and by competing with glucuronidation pathways. The depletion of glutathione (e.g. alcohol abuse) leads to an accumulation of oxidative toxic $NAPQ_1$, resulting in hepatoxicity. Fasting reduces the cofactors needed for glucuronidation and sulfation, depletes hepatic glutathione, and induces CYP 2E1. Alcohol also increases the expression of CYP 2E1, and depletes glutathione. The administered NAC stimulates the hepatic synthesis of glutathione, providing a means to continue the metabolism of acetaminophen without its oxidation to $NAPQ_1$.

When the patient presents with acute liver failure and acetaminophen toxicity is suspected, it is important to start treatment (Table 9) with NAC. Even in non-acetaminophen related toxicity, there is now mounting evidence that NAC provides anti-oxidative benefits and reverses toxic effects in the body. Spontaneous resolution of acetaminophen related DILI is high at 65%, and therefore the need for transplantation in this group is low. Comparatively, non-acetaminophen DILI is associated with 30% spontaneous surivival In patients who do not have spontaneous resolution, risk stratification for emergency liver transplantation   is required (acetaminophen and non-acetaminophen toxicity) (Table 10).
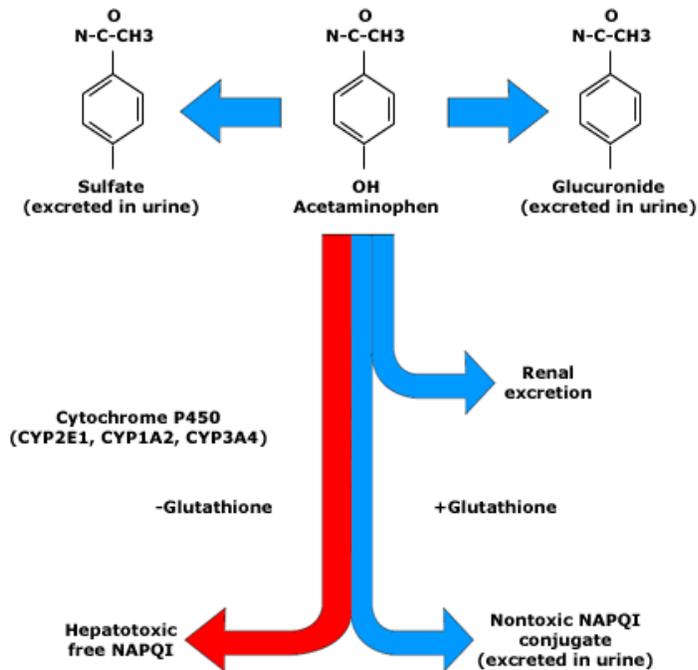
Figure 2. Pathophysiology of acetaminophen toxicity (UptoDate 2011)

Table 9. The management of patients with acetaminophen (ACM) overdose

- ➢ Initial measure
  - o ABC's
  - o Rule out other co-ingestions
  - o Contact liver centre
  - o Serum ACM level, urine toxicology screen, LFT's, INR, arterial lactate
  - o Determine likelihood of hepatotoxicity from normal nomogram (except in non-intentional cases)
  - o Within 4 hrs of ingestion of acetaminophen, charcoal may be given prior to starting NAC

- ➢ Oral N-Acetylcysteine (NAC)
  - o Loading dose: 140 mg/kg po/NG x1
  - o 70 mg/kg q 4 hours x 17 doses
  - o Compazine/raglan for nausea prn
  - o Cimetidine (P450 inducer)

- ➢ IV N-Acetylcysteine (NAC)
  - o Dose 1. Loading dose: 140 mg/kg NAC in 200 ml D5W over 1 hr.
  - o Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 hours.
  - o Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 hrs.
  - o Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hrs.
  - o Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hrs.

- ➢ Caution
  - o Do not administer NAC to patients with known sulfa allergy
  - o Administer IV formulation of oral NAC through a leukopore filter in a monitored setting after consent obtained from patient/family.
  - o IV infusion of NAC leads to anaphylactic/hypersensitive reactions in 3 to 5% most commonly during loading dose.
  - o Hold and reduce infusion rate by 50% if rash/nausea occurs (rare). Administer fluids, IV Benadryl, IV steroids as needed.

- ➢ Psychological assessment

- ➢ Seek transplant centre assessment if hepatic failure (encephalopathy of grade 1 → 4, ATN, hepatorenal syndrome, jaundice, coagulopathy)

Table 10. The King's College risk stratification criteria for liver transplantation in Acute Liver Failure

- ➢ Acetaminophen
  - o INR > 6.5 (PT > 100 sec), serum creatinine > 3.4 mg/dl, stage 3 or 4 encephalopathy
  - o Arterial lactate > 3.5 4 hours after resuscitation
  - o pH < 7.30 or arterial lactate > 3.0 12 hours after resuscitation; or
- ➢ Non-acetaminophen
  - o INR > 6.5 (PT > 100 sec); or
  - o Any 3 of the following:
  - o INR > 3.5 (PT > 50 sec)
  - o Age < 10 or > 40 years
  - o Bilirubin > 17.5 mg/dl
  - o Duration of jaundice > 7 days

4.2. Antiretroviral Agents

Hepatic damage is not uncommon with nucleosides and nucleotide reverse transcriptase inhibitors, as well as protease inhibitors. Persons with HIV/AIDS may be co-infected with HBV or HCV. Immune reconstitution following HAART may activate previously inactive HBV. In addition, this person may over-use alcohol, have other types of hepatic infections, lymphoma or other hepatic tumors, HIV infection itself as well as the drugs used to treat HIV/AIDS can induce DILI. Therefore, it is important to consider all these factors, as they contribute to liver damage.

The blockers of reverse transcriptase of HIV inhibit mitochondrial DNA and reduce oxidative phosphorylation. This leads to fatty liver (micro- and/or macrovascular steatosis),

insulin resistance with lactic acidosis and acute liver failure. The onset of these abnormalities will usually be about 6 months into the treatment.

Acute hepatitis occurs in 3% to 30% of persons taking the protease inhibitor ritonavir. Acute liver failure is rare; the unconjugated hyperbilirubinemia seen in 7% of persons given protease inhibitors does not forebode progression to severe cholestasis.

4.3. Aspirin (ASA)

When ASA is given in high dose (blood salicylate > 25 mg/100 ml), and especially to persons with juvenile rheumatoid arthritis or SLE (systemic lupus erythematosus), there may be marked rises in transaminase levels. Fortunately, acute liver failure is rare, and the drug hepatotoxicity resolves when ASA is stopped The ASA damage is dose-dependent, so it is safe to restart ASA but at a lower dose.

4.4. Sulfasalazine and Mesalamines

Salazopyrine (salicylazosulfapyrine) and mesalazine (mesalazine, 5-aminosalicylate) used in persons with Crohn disease or ulcerative colitis cause an increase in serum ALT and AP, as well as rare cases of chronic hepatitis and the formation of hepatic granulomas. Thus, possible drug toxicity must be included in the differential diagnosis of abnormal liver enzymes in persons with IBD (inflammatory bowel disease).

4.5. NSAIDs and Coxibs

Celecoxib, a COX-2 inhibitor, has a sulfa moiety that may result in a cross sensitivity reaction in persons who are intolerant of sulphonamides. NSAIDS may be associated with the development of hepatocellular injury or cholestasis. With Diclofenac, for example, hepatotoxicity occurs in about 5 persons per 10^5 exposed, but clinical hepatitis is uncommon, and fatalities are exceedingly rare.

4.6. H_2- Receptor Antagonists (H_2-RAs) and Proton Pump Inhibitors (PPIs)

Rare cases of mild acute hepatitis, sometimes associate with cholestasis, have been reported with histamine H_2-receptor antagonists. It is not certain if the rare cases of hepaotoxicity reported in persons taking PPIs were actually drug-related.

4.7. Calcium Chanel Blockers (CCBs) and B-Adrenergic Blockers (BBs)

There have been rare case reports of acute hepatitis with calcium channel blockers. While the acute hepatitis seen with beta-blockers is rare, it may be serious.

4.8. Anti Tuberculosis Therapy

For every 100,000 persons given Isoniazid, about 2000 will develop hepatitis, and approximately 150 will die from acute liver failure. After acetaminophen, isoniazid-hepatitis is the second most common reason for the liver transplantation for drug-induced liver injury. The risk of this adverse effect increases with age; infection with HIV, HCV and possibly HBV; chronic alcohol use; malnutrition; as well as intake of acetaminophen, rifampin and pyrazinamide.

It is important to stress that the hepatotoxicity of isoniazid does not relate to the dose or blood level. Because up to one third of persons taking INH will have an elevated serum ALT

within the first 10 weeks of taking the drug, and may fall even with continuation of drug, measuring serum ALT every 2 to 4 weeks may not necessarily detect severe liver damage. It is uncertain if or when blood monitoring should be done. However, for any person on INH who develops clinical symptoms of hepatitis (anorexia, nausea, vomiting, malaise, fatigue, usually within 1 to 26 weeks of staring INH), the drug must be stopped immediately, regardless of the values of LEs and LFTs.

4.9. Anti-fungals

While some 10% of persons on ketoconazole and 5% on fluconazole have abnormal ALTs, symptomatic hepatitis from ketoconazole occurs in only about $10/10^5$ exposed persons, and is usually mild. The severe hepatic necrosis from fluconazole is even less common, but it can cause derangement in all Les (ALT, AST, AP, bili).

4.10. Anti-depressants

TCAs (tricyclic antidepressants) may cause cholestatic injury which is rarely prolonged. SSRI (selective serotonin reuptake inhibitors) have a good safety profile, with only very rare cases of centrilobular necrosis which may be massive or submassive.

4.11. Immunosuppression agents

Azathioprine or methotrexate may frequently be used in persons with chronic hepatitis or inflammatory bowel disease (Crohn disease or ulcerative colitis). Azathioprine hepatitis occurs with a frequency of about $100/10^5$. The <u>dose</u> and <u>duration</u> of therapy do not predict the likelihood of hepatocellular injury, although monitoring of ALT and AP are still generally recommended. The range of possible liver damage is extensive (Table 11).

Table 11. Hepatic damage associated with the use of azathioprine

- ➢ Biochemical changes, asymptomatic

- ➢ Cholestatisis, cholestatic hepatitis with bile duct injury

- ➢ Vascular injury
  - o sinusoidal obstruction syndrome (hepatic venous outflow, previously called veno-occlusuve disease)
  - o Peliosis hepatitis
  - o Nodular regeneration hyperplasia
  - o Non-cirrhotic portal hypertention
  - o Hepatocellular carcinima

The hepatotoxicity with methotrexate can occur with both high and low dose weekly MTX, as used in IBD or RA. The reported incidence of MTX induced ALT riseis14% and 8% for AST. The LEs tend to resolve within one month of discontinuation. Persons with pre-existing liver disease, chronic excessive use of alcohol (3-fold increase risk of hepatotoxicity with MTX intake with consumption of > 15 g alcohol/day), obesity, diabetes, chronic renal disease, use of NSAIDs or vitamin Amay have an increased in the risk of hepatic damage. After a total intake of 5 g (maintenance MTX in Crohn disease is 25 mg/week, 1300 mg/year, so after about 4 years of MTX), the IBD patient would be at risk: about 20% will develop NASH, 3% hepatic fibrosis.

However, clinically significant liver disease is rare. Regardless, all patients are recommended to be on folinic acid to reduce side effect profile. Because change in LEs are neither sensitive nor specific, the clinician needs to depend instead on finding hypoalbuminemia (hyperbilirubinemia and increase INR are rare) or hepatomegaly. It remains disputed how to surveillance these patients, when or if liver biopsy should be performed to detect MTX-associated liver damage. A liver biopsy can be considered if cumulative dose of 1000-1500mg has been achieved. However, the jury is still out.

4.12. Oral Contraceptives
There is a widespread use of oral contraceptive agents in young women, and several cholestatic hepatic toxicities are recognized (Table 12)

Table 12. Hepatobiliary complications of the use of oral contraceptive agents

- o Gallstone
- o Cholestasis
- o Unmasking cholestatic disease such as primary biliary cirrhosis

4.13. Herbal preparations
With the public's enthusiastic use of herbal preparations and the potential for some of these agents to cause hepatocellular injury and even acute liver failure, a careful historical inquiry into use of herbal preparations must be made in any person with abnormal Les or suspected liver disease, or acute liver failure.

5. Drugs causing Chronic Hepatitis

Some drugs such as nitrofurantoin, methyldopa and minocycline may cause chronic hepatitis, especially in older women who have been on the drug for a long interval. The hepatitis usually responds to stopping the offending agent. In another form of chronic drug-associated hepatotoxicity, anti-nuclear and anti-smooth muscle antibodies develop. Again, stopping the offending drug forms the basis for the recommended therapy.

In persons with known cirrhosis, there will be reduced mass of healthy liver cells capable of metabolizing drugs handled by the liver, and the dose of the drug will need to be reduced ("hepatic dosing") (Table 13). In the same token, there are drugs which are relatively contraindicated in persons with liver disease (Table 14). It is unreasonable to commit these long list to memory, but this information would be useful for you to have handy on your iPhone .

Table 13. Drugs for which lower doses are recommended in patients with cirrhosis

o Acetaminophen	o PPIs
o Benzidiazepine	o Repaglinide
o Beta-blockers	o Risperidone
o Cetirazine	o Sertraline
o Fluoxetine	o Topiramate
o Indinavir	o Tramadol
o Lamotrigine	o Valproic acid
o Losartan	o Venlafazine
o Moricizine	o Verapamil
o Narcotics	

Table 14. Drugs which are relatively contraindicated, or which must be used very cautiously in persons with liver disease

o Alcohol	o Naltrexone
o Clonazepam	o Niacin
o Felbarnate	o Pemoline
o Gemfibrozil	o Tacrine*
o Lovastatin and other HMG-Coa reductase inhibitors ("statins")	o Ticlopidine
	o Tolcapone
o Methotrexate	o Zalcitabine
o Metformin	

* in persons with prior jaundice

496
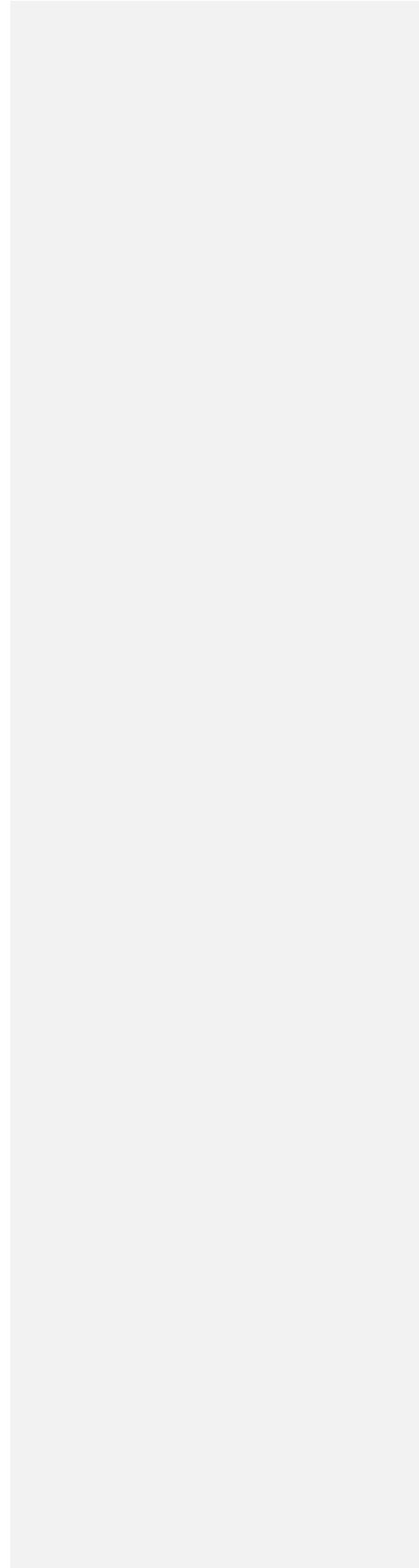
Chapter 26: Cirrhosis and Portal Hypertension
K. S. Gutfreund and A. B. R. Thomson

1. Introduction

There are numerous causes of PHT (portal hypertension), and these can be considered anatomically as pre-hepatic, intrahepatic, and post-hepatic (Figure 7A), or may be considered on the basis of the site of involvement relating to sinusoid: pre-sinusoid, sinusoidal and post-sinusoidal (Figure 7B). In Canada, by far the most common cause of PHT is cirrhosis, ie intrahepatic and sinusoidal. A regenerating nodule will partially block the blood flow in the hepatic sinusoidal and hepatic vein (Figure 8). Note how an internal fistula (anastomosis) forms between the portal vein (PV) and the hepatic vein (HV) at the site of the pre-existing sinusoids (Figure 9A). These regenerating nodules are nourished by blood from the hepatic artery. Note the difference in the structure of the normal acinis (Figure 5), the acinis in cirrhosis (Figure 9A), and in other causes of PHT (Figure 9B). Rarely, no disease process is identified, and idiopathic (primary) PHT may occur (Figure 9C).

With PHT, the normal anatomy of the portal venous system changes dramatically (Figure 10), leading to distention and increased pressure in collaterals which may partially affect the PHT. In time however 50 mg these collaterals may burst and lead to life-threatening bleeding such as from esophageal varices. Note that the paraumbilical anterior abdominal wall veins in PHT flow both upwards and downwards (Figure 11), whereas the flow in distended veins from obstruction of the inferior vena cava do not radiate from the umbilicus, and flow only upwards.

Portal pressure is the product of the portal blood flow in the portal vein (the confluence of the superior mesenteric vein and the splenic vein, and the resistance to blood flow in the lover with PHT, collaterals form in the portal and systemic circulations in the body's attempts to decompress the elevated portal pressure. The development of the collaterals does not usually have any major clinical consequence, except for upper GI bleeding from esophageal varices, or lower GI bleeding from the hemorrhoidal veins. The classification of PHT may be based on whether the disease process is prehepatic, hepatic and posthepatic. A more physiological consideration is whether the cause is presinusoidal (prehepatic and many intrahepatic conditions), postsinusoidal (posthepatic plus two intrahepatic conditions; alcoholic terminal (central) hyaline sclerosis in zone 3, and veno-occlusive disease), or sinusoidal (alcoholic hepatitis or established cirrhosis). The major pathophysiological abnormality in PHT is high-resistance, and it is not clear why high-resistance states are associated with enhanced mesenteric and therefore portal venous flow. The resistance may rise in the liver because of mechanical pressure on the vessels from inflammation, swelling of the hepatocytes, collagen deposited in the space of the Disse, fibrosis and architectural change) or because of the activation of the hepatic stellate cells (aka myofibroblasts, fat storing or Ito cells)leading to vasoconstriction of the sinusoids and elevated microvascular pressure. Presinusoidal causes of the PHT respond well to TIPS or other shunting procedures because the livers function are generally well-preserved because of normal hepatocellular function. Also, ascites does not usually occur with presinusoidal PHT.

The portal disease may be measured directly by the percutaneous insertion of a needle into the portal vein, liver or spleen. Wedging a catheter into the hepatic vein gives the hepatic vein wedge pressure (HVWP), which is an accurate indirect measure of portal pressure. The exception for HVWP being a good surrogate, marker for portal vein pressure is when there is a condition such as portal vein thrombosis causing intrahepatic portal vein resistance, and there will be PHT (portal vein pressure increase, but normal HVWP).

TIPS, transjugular intrahepatic portosystemic stent (shunt); a percutaneously-placed shunt between the hepatic and portal veins, reducing portal vein pressure. For prehepatic cause of PHT (eg, portal vein thrombosis), portacaval or mesocaval shunting will be necessary, in which case hepatic encephalopathy will not develop from the shunting because of the metabolic detoxification capacity of the normal liver parenchyma.

2. Normal anatomy

Before considering what happens to the patient with cirrhosis, we need to review briefly the normal gross anatomy of the liver (Figure 1), including the portal venous system (Figure 2). Blood flows into the liver from the portal vein (PV) (80%) and the hepatic artery (HA) (20%). From the portal vein (PV), blood flows through the sinusoids and into the hepatic vein (HV) (Figure 3). This structure may also be appreciated histologically (Figure 4).

A. Extrahepatic

B. Intrahepatic

Right anterior and posterior branches divide superiorly and inferiorly

Left medial branch divides superiorly and inferiorly

Obliterated umbilical vein
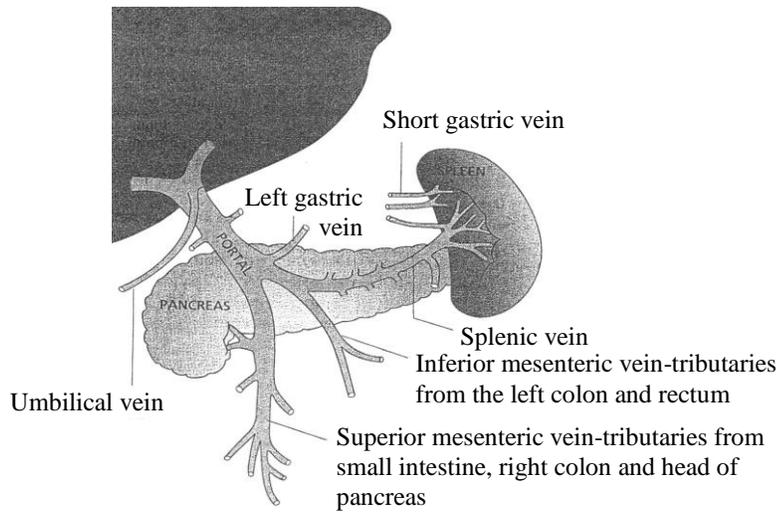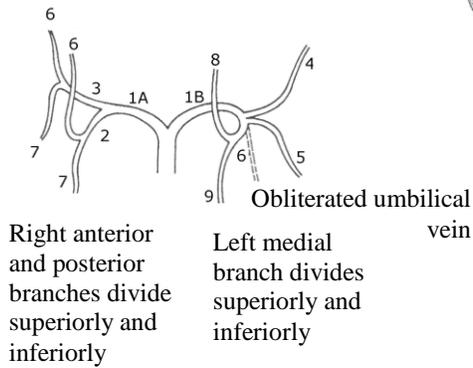
Figure 2. Portal venous system. A). Portal vein is posterior to the pancreas. B). Progressive branching of the intrahepatic portal vein and its distribution to the lobes of the liver. (a) Division into the right and left branches. (b) Division of the right branch into anterior and posterior branches and of left branch into lateral and medial branches. (c) Four segments of liver supplied by the right anterior and posterior and the left lateral and medial branches. (d) Eight final branches of the portal vein.

Adapted from: Sherlock & Dooley, Figure 10.1, page 147, Eleventh Edition, 2002.

First Principles of Gastroenterology and Hepatology   A. B. R. Thomson and E. A. Shaffer
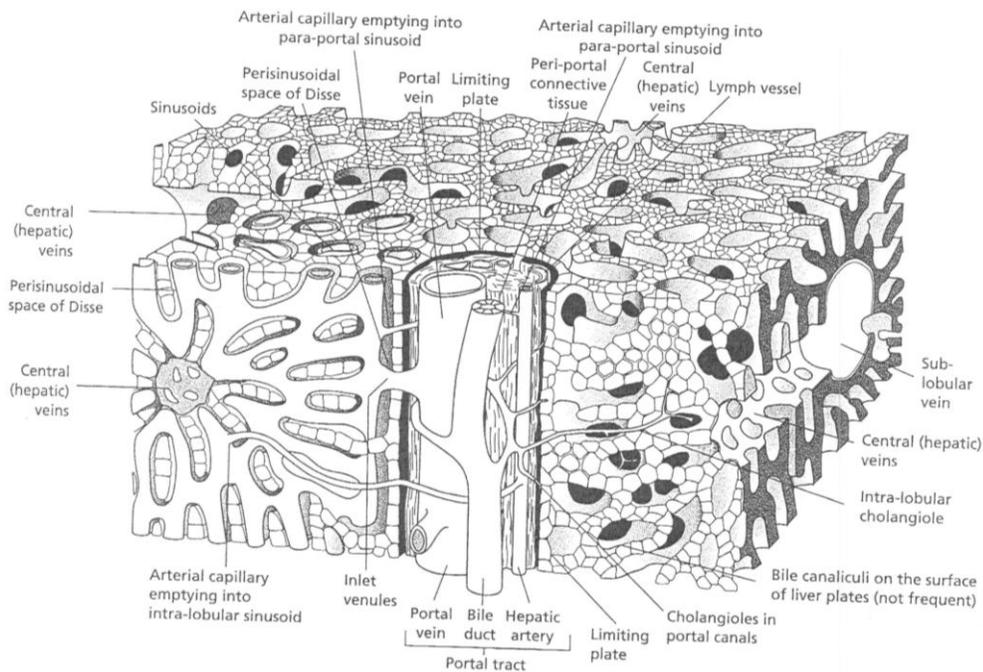
Adapted from: Sherlock & Dooley, Figure. 1.9, pg 7; and Fig 10.42, pg 170, Eleventh Edition, 2002.

There are numerous causes of portal hypertension (Figure 5), the most common of which is the increased portal pressure which occurs as a result of cirrhosis. In cirrhosis, the nodule's blood supply is mostly from the HV, rather than the usual situation of the PV. The nodule obstructs the PV and sinusoids, raising the pressure in the HV and portal venous pressure (Figure 6). Increased Splenic vein blood flow, thrombosis of the Splenic or portal vein will also increase intrahepatic portal pressure, but because these abnormalities are pre-sinusoidal, the HV pressure remains normal (Figure 7).

➢ Heart
o Rise in atrial pressure
  e.g constrictive pericarditis

➢ Inferior vena cava
o Webs, tumour invasion,
  Thrombosis

➢ Hepatic veins
o Large:
  Thrombosis, web,tumour invasion

o Small:
- veno-occlusive disease

Liver

Increased blood flow

Idiopathic tropical splenomegaly
Arteriovenous fistula

Portal vein
Thrombosis invasion
or compression
by tumour

Splenic vein
Thrombosis invasion
or compression
by tumour

'Post sinusoidal'
Veno-occlusive disease
Alcoholic central hyaline sclerosis

Central vein

'Sinusoidal'
Cirrhosis
Non cirrhotic:
Acute alcoholic hepatitis
Cytotoxic drugs
Vitamin A intoxication

C ← → C

S

C ← → C

'Pre sinusoidal'
Schistosomiasis
Early primary biliary cirrhosis
Chronic active hepatitis
Congenital hepatic fibrosis
Sarcoidosis
Toxins; vinyl chloride arsenic, copper
Idiopathic portal hypertension

Portal venule

Figure 5a and b. Causes of portal hypertension. (a) Pre- and post- hepatic. (b) Intra-hepatic (NB an overlap exists; wedge hepatic vein pressure may be high in patients with 'pre-sinusoidal' causes, especially as the disease progresses, indicating sinusoidal and/or collateral involvement. Some 'post-sinusoidal' conditions may also have a sinusoidal component).
Adapted from: *Sherlock & Dooley*, Figure.10.36, page 166, Eleventh Edition, 2002.

A

B
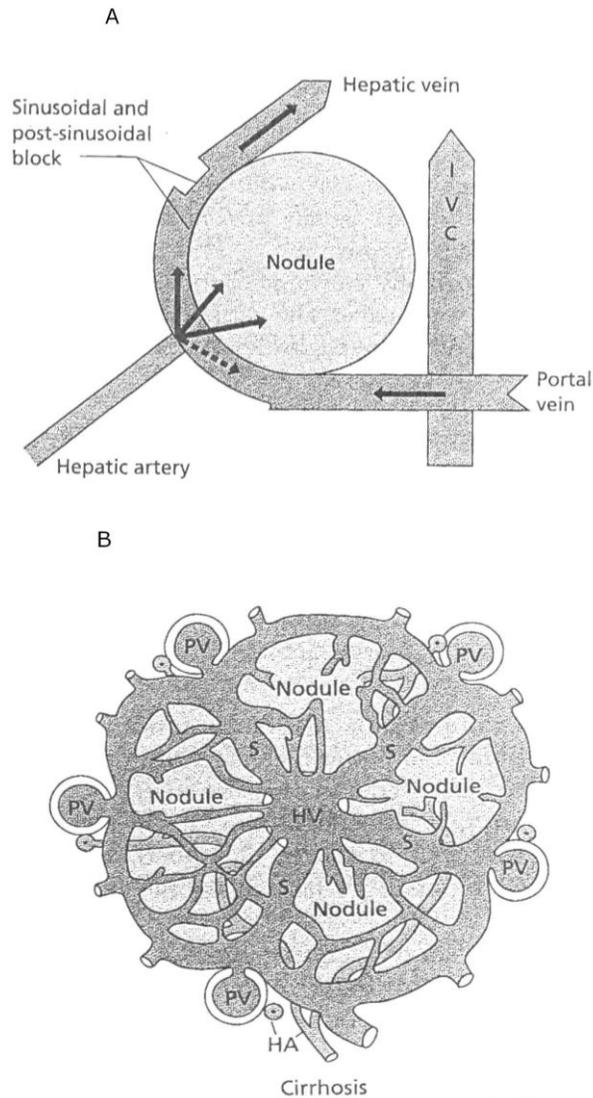
Figure 6. The intrahepatic portion of the hepatic circulation in cirrhosis. (A) A nodule obstructs the sinusoids and hepatic veins. The nodule is supplied mainly by the hepatic artery. IVC, inferior vena cava. (B) Cirrhosis of the liver showing the formation of portal vein (PV)/hepatic venous (HV) anastomoses or internal Eck fistulae at the site of pre-existing sinusoids (S). Note that the regeneration nodules are supplied by the hepatic artery (HA).

Adapted from: *Sherlock & Dooley*, Figure. 10.43, page 170; and Figure. 10.42, pg 170, Eleventh Edition, 2002.
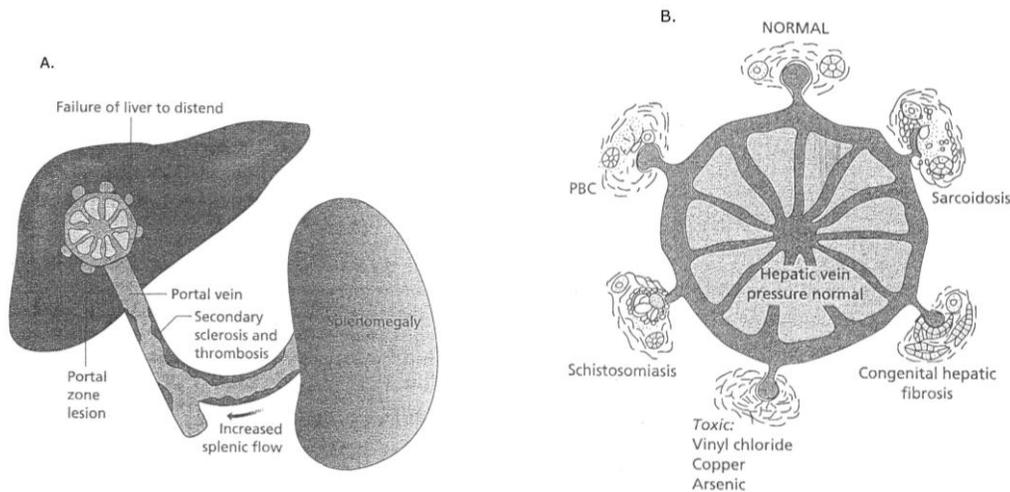
Figure 7. Non-cirrhotic pre-sinusoidal portal hypertension. (A) Idiopathic 'primary' portal hypertension. (B) the etiology of pre-sinusoidal intra-hepatic portal hypertension. PBC, primary biliary cirrhosis.

Adapted from: *Sherlock & Dooley*, Figure 10.40, page168; and Figure 10.41, page 169, Eleventh Edition, 2002.

As a result of the portal hypertension, a collateral circulation develops between the portal and the systemic circulation (Figure 8). While some of these collaterals are a curiosity (Figure 9), life-threatening hemorrhage may develop from the collaterals that develop through the coronary to the esophageal veins, forming esophageal varices (Figure 10). The nodules replace normal hepatic parenchymal tissue, so that with the loss of hepatocytes, there is the loss of the normal functions of the liver, synthesis, secretion and metabolism.

3. Clinical Considerations

Cirrhosis is a pathological condition referring to changes seen on biopsy of the liver in persons with any type of chronic liver disease. Portal hypertentsion (PHT) is a pathological condition in which the pressure in the portal circulation is elevated (>8 mm Hg), usually but not always due to cirrhosis. The clinical presentation of cirrhosis and PHT may overlap for this reason the two conditions will be considered together here. Their serious and important complications (esophageal varices, ascited, hepatorenal syndrome, jaundice, hepatic encephalopathy) will be dealt with in separate chapters.

Cirrhosis may be the end pathological process of most chronic liver disease. The combination of fibrosis, nodules and distortion of the hepatic architecture makes the diagnosis of cirrhosis (Figure). Infection, inflammation, ischemic, and drug/chemical damage begin the process of necrosis of the liver cells, collapse the lobules, and then the development of cirrhosis through fibrosis, nodules and distortion. Once cirrhosis develops, the liver may still have the ability to

repair itself (particularly if the inciting cause of the liver damage is removed), and the cirrhosis may regress.

Cirrhosis is the 5th most common cause of death in the UK and 12th in the USA. Because the prevalence of cirrhosis peaks in the mid- to late-50s, it becomes the 4th most common cause of death in that age group. If the diagnosis of chronic liver disease is made early, there may be effective treatment to prevent the development of cirrhosis, or to at least slow or reverse its progression (Table 1).
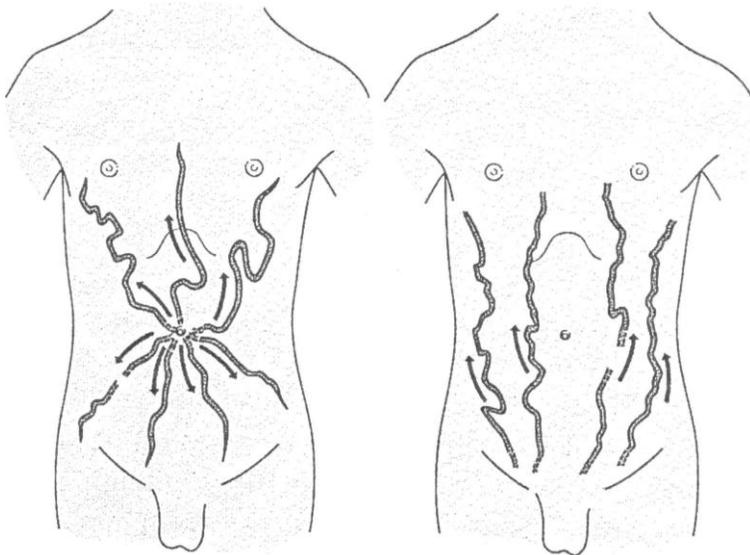
Figure 9. Distrubution and direction of blood flow in anterior abdominal wall veins in portal venous obstruction (left; direction of flow is normal) and in inferior vena caval obstruction (right).

Adapted from: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management* 2006 Fig. 10.11, pg 153.

Table 1. Prognosis of Different Stages of Cirrhosis

Stage	Clinical Perspective	MR
Stage I	compensated, no esophageal varices	1%
II	compensated, with varices	3.4%
III	Ascites	20%
IV	GI bleeding	57%

MR, mortality rate

The portal vein (PV) is formed from the confluence of the splenic vein and the superior mesenteric vein, behind the neck of the pancreas (Figure). The left gastric vein (aka left coronary vein) drains into the confluence of the splenic vein and the superior mesenteric vein. About 75% of blood flow to the liver is from the PV, and 30% from the hepatic artery (systemic circulation). This venous and arterial blood mix in the hepatic sinusoids. The wall of the sinusoids is highly permeable. Blood constituents pass from here into the space of Disse, and from there are taken up by the sinusoidal membrane side of the hepatocyte.

Stellate cells, when activated (for example in cirrhosis and PHT), may contract and worsen the PHT. As PV pressure rises, collateral vessels to the low pressure systemic venous system develop. Also, new vessels develop (angiogenesis) in the body's attempt to lower the PHT. As PHT continues to rise, the PV-systemic collateral circulation develops, such as the left gastric vein and esophageal varices. PHT is caused by both mechanical and vascular factors, with increased intrahepatic resistance (from enhanced intrahepatic vasoconstriction) and increased flow and a hyperdynamic circulatory state (from vasodilation of the splanchnic and systemic systems). The vascular factors are potential therapeutic targets (Table 2).

Table 2. Vascular Factors as Potential Therapeutic Targets

- ➢ Reduce the intrahepatic vasoconstriction
    - o Angiotensin receptor blockers
    - o Mononitrates (nitric oxide [NO])
    - o Anti-endothelin-1, anti- leukotriene, anti-TGF-B (transforming growth factor-B)
    - o Norepinephrine
    - o Serotonin
    - o Thromoboxane drugs

- ➢ Reduce the splanchnic and systemic vasodilation
    - o Nonselective B-adrenergic blockers
    - o Octreotide / vasopressin

- ➢ The two most important future therapeutic targets will likely be to increase the vasodilator nitric oxide (NO), and to decrease the vasoconstrictor endothelin-1 and possibly also the fibrogenic growth factor TGF-B.

These vascular vasoactive factors cause one quarter (25%) of the enhanced portal resistance leading to the PHT in cirrhosis. With the development of cirrhosis, there is the formation of an anastamosis between the portal vein and the hepatic vein (an internal Eck fistulae). The regenerating nodules in cirrhosis are supplied by the hepatic artery.

Truncal zone

Perforating zone (communicate with paraesophageal veins)

Palisade Zone 2-3cm above GE junction

Gastric Zone 2-3 cm below GE junction

Drainage through coronary vein
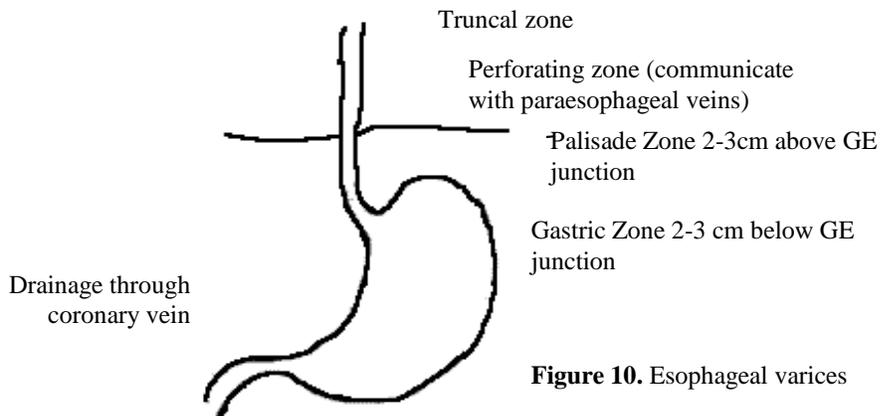
Figure 10. Esophageal varices

The palisade zone is the major area of splanchnic-systemic union, and the location which is most likely for bleeding to occur. Esophageal varices will develop when there is a PV gradient of 10 mm Hg, and will bleed when PV gradient is ≥ 12mm Hg. MRE (magnetic resonance elastography) will measure liver stiffness due to fibrosis, but does not reflect PV pressure. The hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic venous pressure (WHVP) and free hepatic vein pressure (FHVP): WHVP – FHVP = HVPG. HVPG is a useful measure of PHT, used mostly in research or other very specialized settings. HVPG is not valid to assess PV pressure in presinusoidal causes of PHT.

Numerous factors such as chronic alcohol abuse, viral hepatitis (B and C), autoimmune abnormalities, iron overload will stimulate a host of pathophysiological factors to produce necrosis, regenerative nodules and fibrosis (Table 3 and 4). In turn, there will be alterations in the circulation (Table 5), leading to portal hypertension.

Table 3. Causes of cirrhosis

➢ Viral hepatitis
   o HBV, HCV, HDV

➢ Metabolic
   o NASH   o Sclerosing cholangitis
   o Hemochromatosis   o Primary biliary cirrhosis
   o Wilson's disease   o Autoimmune Hepatitis
   o 1-antitrypsin deficiency   o Galactosemia
   o Autoimmune   o Tyrosinemia

➢ Drugs/toxins
   o Alcohol

➢ Conjestive
   o Cardiac failure   o Budd-Chiari

➢ Cystic fibrosis

Adapted from Heathcote J. *First Principles of Gastroenterology* 2005. page 598.

Table 4. Pathophysiological factors responsible for the development of hepatic fibrosis

- o Extracellular matrix proteins (EMP)
- o Hepatic stellate cells (HSC)
- o Activation of HSC to form myofibroblasts
- o Other mesenchymal cell populations and bone marrow-derived cells
- o Hepatocyte growth factor
- o TGF-B
- o Renin-angiotensin system (RAS)
- o Angiotensin-converting enzyme (ACE)
- o Angiotensin I and II receptors
- o Endotoxin, lipopolysaccharide (LPS)
- o Toll-like receptor (TLR4)
- o Angiogenesis
  - − vascular endothelial growth factor (VEGF)
  - − angioporetin 1, 2

Adapted from: Jiao J, et al. *Curr Opin Gastroenterol* 2009; 25: 223-9.

Table 5. The pathophysiological components producing the hyperdynamic circulation and cardiovascular dysfunction in persons with cirrhosis

- ➢ Peripheral and splanchnic arterial vasodilatation
  - o Baroreceptor-induced increase in heart rate

- ➢ Autonomic dysfunction
  - o Increased sympathetic nervous activity
  - o Vagal impairment

- ➢ Alterations in cardiac preload
  - o Increased portosystemic shunting
  - o Increased blood volume
  - o Effects of posture
  - o Decreased blood viscosity

- ➢ Alterations in oxygen exchange
  - o Anemia
  - o Hypoxemia
  - o Hepatopulmonary syndrome
  - o Portopulmonary hypertension

Printed with permission: Møller, S. and Henriksen, J. H. *GUT* 2008; 58: page 271.

There are many causes of cirrhosis, and in the Canadian setting the most common are alcohol, chronic viral hepatitis B and C, and non-alcoholic steatohepatitis (NASA). In perhaps 5-10% of persons with cirrhosis the cause is unknown (idiopathic; aka cryptogenic), perhaps because the initial pathological signs suggesting the etiology (such as NASA) have disappeared, leaving the unhelpful descriptive term cryptogenic cirrhosis

The cirrhotic nodules may be small (micronodular), large (macronodular), or there may be a mixture of the two in micronodular cirrhosis, the septa are thick and there are regular uniformly small regenerating nodules in every hepatic lobule. In macronodular cirrhosis the nodules are of varying size (Figure 30). This pathological distinction is descriptive, and does not imply any diagnosis or prognosis.

Persons with liver disease may present the non-specific generalized symptoms such as weakness or fatigue, specific symptoms suggesting the underlying cause (eg. Alcoholism) of the presence of cirrhosis and symptoms arising form associated PHT (eg. Bleeding, jaundice, confusion, abdominal distention). The patient may have signs of cirrhosis, its complications (decompensate disease) and causes. Once the suspicion of liver disease has been raised, laboratory tests and diagnostic imaging will prove to be useful to confirm the clinical hypothesis that there is liver disease, but the extent of the abdominal liver enzymes such as transglutaminase and alkaline phosphatise, do not reflect the severity of the liver damage. In contrast, the extent of the abdominal blood tests reflect deranged hepatic synthetic or excretory function (albumin, bilirubin, INR) is useful to clarify the severity of the liver disease. For example, the Child-Pugh classification (Table 6) or the MELD score are useful to predict prognosis and help to establish when a liver transplantation may be necessary. For example, the mortality rate from bleeding esophageal varices increase with the Child-Pugh class: A, 15%;B, 25%;C, 50%.

Table 6. The Child's classification of hepatocellular function in persons with cirrhosis

Group designation	A	B	C
o Serum bilirubin (mg/dl)	< 2.0	2.0-3.0	> 3.0
o Serum albumin (g/dl)	> 3.5	3.0-3.5	< 3.0
o Ascites	None	Easily controlled	Poorly controlled
o Encephalopathy	None	Minimal	Advanced (coma)
o Nutrition	Excellent	Good	Poor ('wasting')

Adapted from: Durand F, Valla D. J Hepatol 2005; 42 and Kim, WR et al, *Hepatology* 1999; 29: 1643-8.

When the patient presents with non-specific symptoms such as fatigue and malaise, or symptoms from the course of the liver disease or its complications, when the physical examination shows signs of chronic liver disease, and the liver enzymes (ALT, AST, AP, GGT) and liver function tests (albumin, bilirubin, INR) are abnormal, then further blood tests are performed to establish the cause of the liver disease (e.g. HBV, HCU, ferritin, caeruloplasmin, AMA, quantitative immunogobulins), as well as diagnostic imagine (e.g. abdominal ultrasound with/without Doppler ultrasound), and when tolerated, liver biopsy (Table 7). The clinical examination must be detailed to look for manifestations of disease beyond the liver itself (Table 8). Depending upon the initial clinical findings, the search for the cause of the liver disease may need to be considered (Table 3). Indirect indications of the presence of cirrhosis may

be found on diagnostic imagery (Table 9). The stage of cirrhosis must be established (Table 6). In later chapters, individual conditions are considered, including the management, but all patients with cirrhosis must be considered for preventive care (Table 10), including special precautions if a cirrhotic patient requires an operative procedure (Table 11).

Table 7. The detailed laboratory and diagnostic imaging investigation of the patient with suspected chronic liver disease

- History and physical examination
  - Fatigue, malaise, anorexia, fever, weight loss/gain, ankle swelling
  - Following blood donation-positive hepatitis B or C test
  - Blood transfusions
  - Drug abuse
  - MSM
  - Extrahepatic manifestations (see question 2)
  - Following acute hepatitis-failure of recovery, whether clinical or biochemical or both
  - Abnormal liver enzyme or function tests, or positive hepatitis B or C markers at routine check-up
  - Abnormal physical findings
    - Hepatomegaly,
    - Signs of portal hypertension, splenomegaly, jaundice, peripheral edema, ascites, hepatic encephalopathy, renal dysfunction, bleeding (varices, coagulopathy)
    - Liver – big/normal/small
  - Cutaneous and endocrine changes
    - Spider nevi, palmar erythema, Dupuytren's contractures
    - Gynecomastia, testicular atrophy, impotence
    - Amenorrhea
    - Parotid enlargement
  - Coagulopathy
    - Hypoprothrombinemia
    - Thrombocytopenia
    - Dysfibrinogenemia
    - Slit lamp Kayser-Fleisher rings
  - Circulatory changes
    - Hyperdynamic circulation
    - *Arterial desaturation, clubbing

- Laboratory tests
  - Liver function tests
    - Bilirubin
    - Aspartate transaminase (AST; SGOT)
    - Alanine transaminase (ALT; SGPT)
    - Gamma-globulin
    - Albumin
    - Alkaline phosphatase (ALP)
    - Gamma glutamyl transferase (GGT)

- o Hematology
  - – Hemoglobin
  - – White cell count
  - – Platelet count
  - – Prothrombin time
  - – PPT
- o Special tests
  - – Serum antibodies
    - ▪ Nuclear
    - ▪ Smooth muscle
    - ▪ Mitochondrial
    - ▪ Liver/kidney microsomal
  - – HBsAg
  - – HBeAg
  - – HBeAb
  - – Anti-HCV and HCV RNA
  - – Serum iron, transferin, % saturation, genetic testing
  - – Serum ferritin
  - – Serum ceruloplasmin as well as blood and urinary copper
  - – Alpha-fetoprotein
  - – Creatine kinase (if smooth muscle disease suspected as cause of ↑ALT/AST fasting total, LDL, HDL cholesterol, triglycerides
  - – Protein electrophoresis (polyclonal ↑ gamma globulins in AIH)

➢ Abdominal ultrasound, CT, fibroscan

➢ Core liver biopsy
  - o Hematoxylin and eosin, connective tissue stains, "special stains"

Source: ABR Thomson. *GI Practice Review*: CAPstone Publishing. 2010.

Table 8. Clinically significant extrahepatic manifestations of acute and chronic liver disease

➢ CNS: depression, anxiety, HE

➢ Lung: portopulmonary hypertension, hepatopulmonary syndrome, pleural effusion, congestive heart failure

➢ Heart: prolonged QT (from low Mg^{2+}), endocarditis, ↓ systemic vascular resistance, arterial BP ↑, HR, CO, peripheral intravascular vasodilation

➢ Blood: Coagulopathy (VK, DIC, fibrinolysis), thrombocytopenia, Hypersplenism, ↓ thrombopoetin, immune mediated destruction, ITP (esp interferon for HCV), direct effect of alcohol, cryoglobulinemia

- ➢ GI
  - ○ esophageal ulcers from sclerotherapy, GERD, varices
  - ○ stomach: delayed gastric emptying, PHG, GAVE
  - ○ small bowel: slow transit, bacterial overgrowth
  - ○ colon: rectal varices

- ➢ Bone: osteoporosis, osteomalacia: cholestasis, liver Tx, malnutrition, alcohol, tobacco, ↓ motility, hypogonadism, malabsorption

- ➢ Renal: hypanatremia; ascites, hepatorenal syndrome, glomerulosclerosis (HCV), nephritic syndrome, amyloid

- ➢ Muscle: spastic paraparesis from demyelination of corticospinal tracts and posterior columns, wasting; arthritis (hemochromotosis)

- ➢ Gonads; hypergonadism, amenorrhea

Source: ABR Thomson. GI Practice Review. *CAPstone Publishing* 2010.

Abbreviations: BP, blood pressure; CNS, central nervous system; CO, cardiac output; DIC, disseminated intravascular coaguloath;, GAVE, gastric antral vascular ectasia; GERD, gastroesophageal reflux disease; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, heart rate; ITP, idiopathic thrombocytopenic purpura; PHG, portal hypertensive gastropathy; VK, vitamin K

Table 9. Hepatic/extrahepatic signs of cirrhosis on hepatic imaging (CT, MR)

- ➢ Hepatic
  - ○ Nodularity
  - ○ ↑ periportal space
  - ○ Posterior notch
  - ○ ↑ caudate and lateral segment
  - ○ ↑ candate-to-right lobe size
  - ○ Enlarged gallbladder

- ➢ Extrahepatic
  - ○ Splenomegaly
  - ○ Varices
  - ○ Ascites
  - ○ Gamma-gandy bodies

Adapted from: Ito, K, et al. *Magn Reson Imaging Clin N Am* 2002; 10(1): 75-92, vi.

Table 10. Management considerations in the pre- and post-operative care of the patient with advanced liver disease

- ➢ Prevention of hepatic encephalopathy (HE)
    - o Avoidance of nephrotoxic insult
    - o Correction of reversible metabolic factors
    - o Oral lactulose administration, titrated to ~3-4 bowel movements per day
    - o Administration of nonabsorbable antibiotics
    - o Supportive care
    - o Avoidance of nephrotoxic insult
    - o Correction of reversible metabolic factors

- ➢ Treat complications of portal hypertension (PHT)
    - o Ascites
    - o Antibiotics
    - o Steroids
    - o Coagulopathy
    - o Vitamin K supplementation (oral or parenteral)
    - o Fresh, frozen plasma transfusions
    - o Intravenous administration of cryoprecipitate
    - o Intravenous administration of recombinant factor VIIa
    - o Platelet transfusions
    - o Paracentesis with analysis of ascitic fluid for evidence of infection
    - o Oral diuretic therapy with spironolactone and/or furesomide
    - o Fluid restriction (if sodium concentration is <120 mmol/l)
    - o Avoidance of excessive saline administration
    - o Albumin infusion (with paracentesis volumes >5l)

- ➢ Diet
    - o Maintenance of an adequate protein intake (1-1.5g/kg per day)
    - o Promotion of a balanced diet
    - o Dietary sodium restriction (<2 g daily)

- ➢ Pain control
    - o Dilandid
    - o Avoid benzodiazepans, NSAIDs, narcotics

- ➢ Assess pulmonary function
    - o Supplemental oxygen

Adapted from: Hanje, A.J., and Pate, T. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4: page 272.

Table 11. The preventive care of the patient with cirrhosis.

➢ Prevention of first variceal hemorrhage EGD q3 years, with banding or beta blockers (primary prophylaxis)

➢ Prevention of recurrent variceal hemorrhage (secondary prophylaxis)
  o Beta-blockers
  o Banding
  o Sclerotherapy
  o Shunts (TIPS)

➢ Prevention of bacterial infections after GI bleeding (antibiotic prophylaxis)

➢ Prevention of SBP (antibiotics for previous SBP)

➢ Statins, anticoagulation

➢ Assess for minimal (subclinical) HE (grade 0), and treat appropriately; testing for driving competence

➢ Vaccination – Influenza, Pneumococcus, HAV, HBV

➢ Nutrition assessment and treatment

➢ Avoid alcohol, Viagra, vasodilators, NSAIDs, hepatotoxic herbs, benzodiazepines

➢ Education, family counseling

➢ Screening for CEA, DM, HBP, HCC, osteoporosis, diabetes, hypertension, HCC; usual screening for breast, prostate, cervix, colon

➢ Medialert bracelet

➢ Ongoing evaluation for possible liver transplantation

While the investigation of the patient with possible liver disease may at first appear to be difficult, in fact the clinician needs to ask her/himself only four questions:

Table 12. Does the person have liver disease?

1. Does the clinical presentation suggest that the person has liver disease?
  ➢ Symptoms
    o General
      – Weakness
      – Fatigue
    o Specific
      – Underlying disease
      – Cirrhosis/PHT

  ➢ Signs
    o Examining the patient
    o Abdomen

  ➢ Diagnostic Imaging

2. Do laboratory tests suggest the presence of liver disease?
   - Liver Enzymes (LEs)
     - Hepatocellular: ALT, AST
     - Cholestatic: AP, 5'NT, GGT

   - Liver Function Test (LFTs)
     - Albumin
     - INR
     - Bilirubin

3. What laboratory tests are done to determine the etiology of liver disease?
   - Infection
     - Viral: A,B,C,D,E…EBV, HSV
     - Bacterial

   - Infiltration
     - Fe, Cu, FAT (cholesterol, TG, blood sugar)
     - RBC, WBC
     - HCC

   - Immune
     - AMA (anti-mitochondrial antibody)
     - Quant, immunoglobulins
     - ATG (anti-transglutaminase)

   - Inherited
     - Cystic fibrosis
     - α1-antitrypsin deficiency

4. What is done to determine the cause of liver disease?

   - Ultrasound ($\pm$Doppler)

   - HIDA scan

   - MRCP

   - CT

Biopsy: US'/CT-guided percutaneous biopsy

With this simple approach: 90% of diagnoses of Liver Disease

4. Management of Cirrhosis, and Portal Hypertension

The response to treatment and the possibility of removing the etiological agent of the chronic liver disease will determine the prognosis.

Even with mild cirrhosis (Stage I), progression to a more severe stage occurs at the rate of about 11 % per year. This progression leads to the complications of portal hypertension (PHT) developing and causing death from bleeding esophageal varices, ascites and renal failure, encephalopathy, infection and hepatocellular cancer (HCC). Since the high mortality rate in cirrhosis is from the complications of PHT, we need to consider the role of preventive therapy of cirrhosis with NSBBs (non-selective beta blockers), antibiotics, statins and anticoagulants.

4.1. Non-selective beta blockers

NSBBs such as propranolol (80 mg bid)or nadolol reduce PHT and splanchnic as well as systemic arterial vasodilation which result from the progressing fibrosis associated with hepatic necrosis, and nodular regeneration. While the portal venous pressure progresses, the risk of complications also increases. The HVPG (hepatic venous pressure gradient) is a useful clinical tool as a surrogate marker for portal venous pressure and the prognosis from PHT (Table 13). Note that HVPG is not valid to asses PV presence in presinusoidal causes of PHT.

Table 13. Prognostic Use of HVPG in Cirrhosis

HVPG, mm Hg	
< 10	o 90% 4-year survival without hepatic decomposition
>10	o 40% 4-year survival without hepatic decomposition
<12, or	o Reduced risk of first and further episodes of variceal bleeding
≥ 20% of baseline	o Reduced risk of ascites, SBP (spontaneous bacterial peritonitis) and HRS (hepatorenal syndrome)
	o Reduced mortality rate

It is important to note that while these improvements are, certainly partially due to the beneficial effect of NSBBs reducing PHT (HVPG), there appears to be an additional benefit of NSBBs independent of improved liver functions. For example, NSBBs reduce the risk of SBP in cirrhosis. Antibiotics (see below) also prevent recurrence of SBP, but curiously also reduce HVPG and reduce the likelihood of rebleeding after an acute variceal hemorrhage.

4.2. Antibiotics

Of course antibiotics are useful to treat infections in persons with cirrhosis and PHT. Antibiotics also can be used to reduce the risk of recurrence of SBP, the risk of recurrent acute variceal bleeding, the risk of HRS (especially in cirrhotics with ascites which has a low albumin concentration), and the treatment and risk of recurrence of hepatic encephalopathy (Table 14). It is not certain what is the mechanism by which antibiotics reduce HVPG.

Table 14. Beneficial Role of Antibiotics in Cirrhosis

Treatment and prevention	SBP, HE
Prevention	HRS, rebleeding EV

Abbreviations: EV, esophageal varices; HRS, hepatorenal syndrome: HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis

The combination of NSBB plus antibiotic (e.g. propanolol 80 mg bid plus norfloxacin 400 mg/d) reduce hospitalizations, morbidity and mortality in cirrhotics, and are highly cost-effective.

4.3. Statins

Statins, like antibiotics and NSBBs, have benefits beyond their primary therapeutic use of blocking HMG-CoA reductase, thereby reducing cholesterol synthesis and LDH cholesterol levels. Statins also reduce HVPG and improve liver function as well as reduce the risk of the development of HCC. The mechanism of this beneficial effect is unkown.

4.4. Anticoagulation

It might appear to be counterintuitive to use an anticoagulant in a cirrhotic patient with a prolonged INR and with esophageal varices. However, the coagulopathy in cirrhosis involves both pro- and anticoagulant factors by similar amounts, resulting in normal thrombin generation. Anticoagulants act on hepatic stellate cells to reduce hepatic necrosis and fibrosis, and warfarin is currently being studied in a randomized controlled trial in persons with a liver transplantation for HCV. Enoxaparin reduces the risk of the cirrhotic developing portal vein thrombosis, and oral anticoagulation may be used in a cirrhotic to reduce the risk of extension of an established portal vein thrombosis (treatment of associated esophageal varices must preclude anticoagulation).

Chapter 27: Ascites and Spontaneous Bacterial Peritonitis
F. Wong

1. Ascites

1.1. Introduction

Ascites is the detectable collection of free fluid in the peritoneal cavity. The risk of developing ascites after the diagnosis of cirrhosis is approximately 60% over 10 years. The five-year survival after the onset of ascites is only 50%. This is reduced to two years survival with the development of refractory, or diuretic-resistant ascites. This contrasts with a survival rate of 80% in two years following liver transplantation. Ascites also predisposes patients to life-threatening complications such as spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome. Therefore, the development of ascites is an indication for referral for assessment for liver transplantation.

1.2. Pathophysiology

Sodium retention is central to the development of ascites. What leads to the development of sodium retention in cirrhosis is controversial. There is now ample evidence to support that sodium retention in cirrhosis, although subtle, actually begins before the development of ascites. At the pre-ascitic stage of cirrhosis, erect posture induces sodium and hence water retention via the activation of the intrarenal renin-angiotensin. Other mechanisms that contribute to sodium and hence water retention in pre-ascitic cirrhosis include the loss of glomerulotubular balance and possibly increased cell mass of the thick ascending limb of Loop of Henle, which contains the Na^+-K^+-$2Cl^-$ co-transporters. When the patient assumes the supine posture, there is redistribution of the excess volume to the upper part of the body. This leads to atrial natriuretic peptide (ANP) levels increasing to help improve renal sodium excretion in the supine position. The circulation also vasodilates and becomes hyperdynamic in the supine position. Cardiac output increases and renal perfusion improve, as well as secretion of some of the excess sodium.. However, the increased ANP levels and the supine posture are insufficient to eliminate all the sodium retained in the upright posture. Eventually, the pre-ascitic cirrhotic patient will come into a new state of sodium balance at the expense of an expanded intravascular volume.

As the cirrhotic process progresses, further changes in the circulation occur. The hyperdynamic circulation, which is only present in the supine posture in the pre-ascitic stage, becomes more obvious and eventually appears also in the erect posture. The hyperdynamic circulation is the result of increasing vasodilatation occurring both in the splanchnic and the systemic circulations, due to the presence of excess vasodilators. In the "Peripheral Arterial Vasodilatation Hypothesis," it is proposed that, in cirrhosis, arterial vasodilatation leads to a decrease in splanchnic and systemic vascular resistance. The vasodilation and decreased resistance cause pooling of blood in the splanchnic circulation, resulting in a reduction of the effective arterial blood volume. This in turn further activates various neurohumoral pressor systems to increase renal sodium and water retention in an attempt to restore the effective arterial blood volume and to maintain blood pressure. However, the renal circulation is exquisitely sensitive to the vasoconstrictive effects of these neurohumoral pressor systems, and the glomerular filtration rate (GFR) decreases. This further enhances renal sodium retention. When the increased renal sodium and water retention cannot keep pace with the arterial vasodilatation, there follows a cascade of further activation of neurohumoral pressor systems follows, leading to further sodium and water retention.

Hepatic dysfunction also stimulates renal sodium retention, through some yet undefined mechanism, as sodium excretion has been shown to be related to a threshold of hepatic function. The presence of sinusoidal portal hypertension stimulates renal sympathetic activity, enhancing

renal sodium retention. Sinusoidal portal hypertension also preferentially localizes the excess fluid to the peritoneal cavity as ascites (Figure 1).

Pathophysiology of Ascites Formation
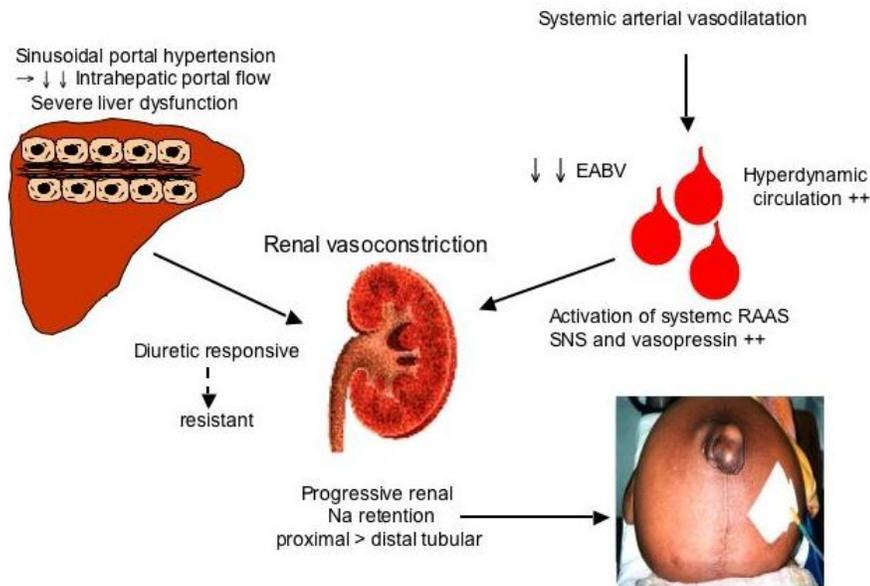
Figure 1. Pathophysiology of ascites formation. EABV = effective arterial blood volume, RAAS = renin-angiotensin-aldosterone system, SNS = sympathetic nervous system.

1.3. Clinical Presentation

The first clinical evidence of ascites is body weight gain. Peritoneal fluid of less than 2 litres is difficult to detect clinically, but abdominal ultrasound is useful in defining small amounts of ascites of ≤500mL. As the volume of ascites increases, the abdomen becomes distended, often with fullness (bulging) in the flanks. Bulging flanks and the presence of flank dullness are the most sensitive physical signs for ascites, whereas eliciting a fluid wave or confirming shifting dullness are the most specific. Complications related to ascites and increased intra-abdominal pressure, such as umbilical hernia may be present. Scrotal and leg edema are found with severe fluid retention. A pleural effusion can accompany ascites, and it is usually on the right side. This is due to the presence of a normal diaphragmatic defect, which allows ascitic fluid to pass into the pleural cavity. Occasionally, only a pleural effusion is present without any ascites.

Patients will also demonstrate signs and symptoms of a hyperdynamic circulation, such as systemic hypotension, resting tachycardia and warm periphery, as well as evidence of portal hypertension such as distended abdominal wall veins radiating from the umbilicus. Other complications of cirrhosis such as jaundice and muscle wasting, which can be quite profound, may also be present.

Examination of ascitic fluid by diagnostic paracentesis should be performed at the patients first presentation, or when there is alteration of the patient's clinical state, such as a sudden increase in the amount of ascitic fluid, worsening of hepatic encephalopathy, abdominal pain, or the presence of fever (Table 1). Diagnostic paracentesis is performed to rule out other complications of the cirrhosis such as spontaneous bacterial peritonitis (SBP), hepatocellular carcinoma (HCC), or other non-cirrhotic causes of ascites (Table 2). Ascitic fluid analysis should include a total polymorphonuclear (PMN) count; protein, albumin, glucose, and lipase concentrations, and bacterial cultures. Exactly 10 mL of ascitic fluid should be directly inoculated into blood culture bottles at the bedside. This increases the diagnostic yield from 50% to >80% when the PMN count is >250 cells/μL, which is diagnostic of SBP. Variants of SBP are shown in Table 3.

Table 1. Indications for diagnostic paracentesis

- ➢ New Onset Ascites
- ➢ Hospital Admission of the Cirrhotic Patient
- ➢ Development of:
  - o peritoneal signs/symptoms eg. fever, abdominal pain
  - o alterations in GI motility
  - o encephalopathy
  - o renal insufficiency
- ➢ Ascitic Patient with GI Hemorrhage

Table 2. Causes of Ascites

- ➢ Cirrhosis from any etiology (75%)
- ➢ Malignancies (15%)
  - o Carcinoma of stomach
  - o Carcinoma of colon
  - o Pancreatic carcinoma
  - o Hepatoma with or without cirrhosis
  - o Metastatic intra-abdominal malignancies
  - o Hodgkin's and non-Hodgkin's lymphoma
  - o Ovarian carcinoma and Meigs' Syndrome
- ➢ Heart failure (3%)
- ➢ Tuberculosis (2%)
- ➢ Pancreatitis   (1%)
- ➢ Others (5%)
  - o Acute Budd-Chiari syndrome
  - o Nephrotic syndrome
  - o Myxoedema
  - o Ovarian hyperstimulation (result of in vitro fertilization)

The appropriate frequency of a given cause of ascites is given in brackets.

Table 3. Variants of Spontaneous Bacterial Peritonitis (SBP)

	Ascitic Fluid Analysis	
	PMN count	**Organisms**
➤ Spontaneous Infection		
o Spontaneous Bacterial Peritonitis	>250 cell/µL	single
o Monomicrobial nonneutrocytic bacterascites (MNNB)	<250 cell/µL	single
o Culture-negative neutrocytic ascites (CNNA)	>250 cell/µL	negative culture
➤ Secondary Infections	>250 cell/µL	multiple

A serum-ascitic fluid albumin gradient (SAAG) of >11 g/L has a >97% accuracy in predicting cirrhotic ascites. Likewise, a SAAG of <11 g/L confers a >97% accuracy in excluding portal hypertension as a cause of the ascites. A high protein content may be associated with congestive heart failure, or Budd-Chiari syndrome (occlusion of the hepatic vein), and may also be seen in pancreatic ascites. Of note, a low ascitic protein concentration (<10 g/L) puts the cirrhotic patient at increased risk for developing SBP. Either abdominal ultrasound or CT scan of the abdomen may be used for the detection of ascites. In particular, abdominal ultrasound can detect even a few mLs of ascitic fluid and is highly sensitive (>95%) and specific (>90%). Abdominal ultrasound may also be used to establish the optimal site in which to perform the paracentesis, and will show the size of the liver and spleen.

1.4. Management

An algorithm for the management of ascites is given in Figure 3. Treating the underlying etiology of cirrhosis has the potential to reverse the associated hepatic decompensation, thus the management of cirrhotic ascites begins with the treatment of the etiologic factors, if possible, such as abstinence from alcohol. Patients with decompensated cirrhosis from hepatitis B should be treated with antiviral therapy. Although bed rest will result in redistribution of body fluid, salt and fluid restriction is required to mobilise the ascites. The patient is usually prescribed a low salt diet containing 44-66 mmol sodium per day, which is even lower than that contained in a no-added salt diet. Professional dietary advice is necessary, and patients require specific instructions regarding where to purchase low salt food. Salt substitutes are contraindicated, as they often contain potassium chloride, and therefore predispose the patients who are taking potassium-sparing diuretics to the development of hyperkalemia. Patients should be carefully monitored with daily weights and with frequent 24-hour urinary sodium excretion measurements. The rate at which ascitic patients gain or lose weight can be used to assess compliance with the low salt diet, and the efficacy of diuretic treatment (Table 4). The urinary creatinine is measured simultaneously with as the urinary sodium to assess completeness of the urine collection. Random urine sodium assessments are unreliable, as urine sodium excretion varies over the course of the day. However, a urine Na^+/K^+ ratio of >1 predicts with 95% accuaracy a urinary Na^+ excretion of >78 mmol/day. Measurement of abdominal girth is unreliable as gaseous distension is common.

Table 4. Predicting weight change in patients compliant with low salt (44 mmol Na/day) Diet

➢ Scenario I	o Urinary sodium excretion is 100 mmol/day
	o Na intake = 44 mmol/day
	o Na output = 100 mmol/day
	o Na balance = (44-100)mmol/day
	$\quad\quad\quad\quad$ = -56 mmol
	o Ascitic [Na] = 130 mmol/L
	o Therefore fluid loss = -56 mmol / 130 mmol/L
	$\quad\quad\quad\quad$ = -0.41 L
	o weight loss/day = 0.41 kg
➢ Scenario II	o Urinary Sodium Excretion 0 mmol/day
	o Na intake = 44 mmol/day
	o Na output = 0 mmol/day
	o Na balance $\quad$ = (44-0) mmol/day
	$\quad\quad\quad\quad$ =+44 mmol
	o Ascitic [Na] = 130 mmol/L
	o Therefore fluid loss $\quad$ = +44 mmol / 130 mmol/L
	$\quad\quad\quad\quad$ = 0.34 L
	o weight gain/day = 0.34 kg

Diuretic therapy, in addition to salt and fluid restriction, will be required in 90% of cirrhotic patients to manage their ascites. Spironolactone, a distal diuretic with anti-aldosterone activity, is the preferred first line diuretic. This is because ascitic patients usually have hyperaldosteronism. Furthermore, any sodium reabsorption that is blocked by loop diuretics at the Loop of Henle will be reabsorbed when the sodium is delivered to the distal tubule. Combination diuretic therapy, with both a distal potassium sparing and a loop diuretic, acting on two different sites of the nephron, is now the standard of care. The combination approach has been proven to be more effective than sequential use of different classes of diuretics in the elimination of ascites. Spironolactone is usually started at a dose of 100 mg/day. Spironolactone has a slow onset and offset of action because its half-life in cirrhotic patients can be as long as 35 hours. Therefore, frequent dose adjustments are unnecessary, and patients should still be monitored even after spironolactone is discontinued. One of the unacceptable side effects of spironolactone is painful gynecomastia in men.

Amiloride, another potassium-sparing diuretic, is a less potent but certainly acceptable alternative to spirolactone. The starting dose is 5 mg/day. Either potassium-sparing diuretic is usually combined with furosemide, starting at 40 mg/day. The combination can be increased in a stepwise fashion (Table 5).

Table 5. Step-wise approach to the use of diuretic therapy for the management of ascites *

	I	II	III	IV
➢ Spironolactone/	100 mg	200 mg	300 mg	400 mg
➢ Amiloride	5 mg	10 mg	15 mg	20 mg
➢ Furosemide	40 mg	80 mg	120 mg	160 mg

* Monitor: daily weights
              weekly postural symptoms/signs
              twice weekly electrolytes, renal function
              symptoms/signs of encephalopathy

Increase diuretics if: weight loss < 1.5 kg in 1 week, and if patient is compliant with low Na diet, and if renal function is normal, and no electrolyte abnormalities or hepatic encephalopathy.

Electrolyte abnormalities and renal dysfunction are common in cirrhotic patients on diuretics, and should be monitored regularly. Initial outpatient management may be attempted if the volume of ascites is small, and when the ascites occurs in the absence of complications such as concomitant gastrointestinal hemorrhage, encephalopathy, infection or renal failure. Hypokalemia and hypochloremic alkalosis can precipitate hepatic encephalopathy, and should be avoided by the use of juicial changes in the dose of diuretics. Too rapid mobilization of fluid will result in worsening of renal function.

Patients with peripheral edema can have their fluid mobilized more rapidly, as the edema fluid can easily be absorbed to replenish the intravascular volume. The dose of diuretic should be reduced if there are symptoms of encephalopathy, a serum sodium ≤125mmol/L, or a serum creatinine of ≥130mmol/L. Initially, daily weights and at least twice weekly electrolytes and renal function should be monitored. Urine sodium excretion must be greater than the oral sodium intake in order for the patient to lose weight. Weight loss of greater than 0.5 kg/day should be discouraged. This is because the amount of ascitic fluid that can be mobilized each day is ≤ 700 mL. Therefore, weight loss of >0.5kg per day usually means loss of fluid from the circulatory volume, thus predisposing the patient to the very unwanted development of renal failure.

Refractory ascites is defined as ascites unresponsive to 400 mg of spironolactone or 30 mg of amiloride plus up to 160 mg of furosemide daily for two weeks, in a patient who has been compliant with sodium restriction. Non-compliance with sodium restriction is a major and often overlooked cause of so-called "refractory" ascites. Other causes of refractory ascites include the development of SBP, hepatocellular carcinoma (HCC), and intrinsic renal pathology. Refractory ascites without any underlying cause usually indicates a grave prognosis, with only 50% survival at 6 months.

Large volume paracentesis is now recognized as a safe and effective therapy for the treatment of refractory ascites. In one large randomized controlled trial, large volume paracentesis was safer and more effective than was diuretic therapy for the management of ascites, with reduced length of hospitalization. There was, however, no survival advantage of paracentesis over diuretic therapy for the ascites.

Removal of ascitic fluid volume of up to 5 litres without the simultaneous infusion of plasma expanders is safe, even in non-edematous patients. Larger volumes can be removed at one sitting in edematous patients. Albumin infusion of 6-8 g per litre of ascitic fluid removed has been recommended for repeated large volume paracenteses of >5litres. This is because patients may develop a post-paracentesis syndrome known as "circulatory dysfunction". This is characterized by a further rise in renin-angiotensin activity, and potentially the development of renal impairment. The risk factors for the development of post-paracentesis circulatory dysfunction are unknown.

There is still some controversy regarding the use of albumin post-paracentesis, as patients who do not receive albumin have not been shown definitively to have greater mortality. Other plasma expanders, such as Hemaccel, Dextran 70 and Pentaspan, have also been used and have been shown to be equally effective. However, a group in Barcelona has suggested that albumin is superior to all the other volume expanders in the prevention of post-paracentesis circulatory dysfunction and the development of renal failure. A recent study from Toronto has shown that as long as the ascitic volume removed is less than 8 litres and the standard dose of albumin of 6-8 gm per litre of ascitic fluid removed is given, the development of post-paracentesis circulatory dysfunction is not associated with any renal dysfunction. This represents the standard of CARE in Canada.

Vasopressin receptor antagonists, which are pure aquaretic agents, have been tried in combination with diuretics and large volume paracentesis in the management of ascites, whether the patient is still diuretic-responsive or diuretic-resistant. Vasopressin receptor antagonists are able to reduce the volume of ascites accumulated, and hence the frequency of large volume paracentesis in these patients.

A transjugular intrahepatic portosystemic stent shunt (TIPS) is an effective means of managing refractory ascites. A communication is created between a branch of the portal vein and a branch of the hepatic vein, and this communication is held open by a metal stent. This stenting reduces the sinusoidal portal pressure, and allows a slow but effective elimination of ascites. There are five published randomized controlled trials showing that TIPS is better than large volume paracentesis in the control of ascites. Without the use of diuretics, sodium excretion begins after the first month, and slowly increases thereafter. Within 6 months, complete resolution of ascites eventually occurs in approximately two-thirds of patients, and a partial response in the other third.

Unfortunately, patients with advanced liver disease have higher morbidity and mortality after TIPS, so that placement of a TIPS is not recommended for patients with a Child-Pugh score of >12 or a Model for End-Stage Liver Disease (MELD) score of >14. Elderly patients with cirrhotic ascites also fare less well with a TIPS. Predictors of early mortality from a TIPS include active bleeding at the time of TIPS insertion for ascites, a prior history of hepatic encephalopathy, significant jaundice (bilirubin >51 µmol/L), and elevated transaminases (ALT >1000 IU/L). Absolute contra-indications to TIPS insertion include ongoing high-grade encephalopathy, cardiac or intrinsic renal disease, non-compliance with sodium and water restriction, and the very elderly (> 70yrs).

The major complications of TIPS are shunt stenosis and hepatic encephalopathy. Therefore, regular assessments of shunt patency with doppler ultrasound and/or angiography are required. In recent years, the use of covered stents has significantly reduced the rate of shunt stenosis. Also, prophylactic use of lactulose can reduce the incidence of post-TIPS encephalopathy. If the serum bilirubin increases post-TIPS insertion, shunt hemolysis should be considered, in addition to worsening liver function.

In the patient who is suitably selected for a TIPS, the result can be very gratifying, with improved nutritional status once the ascites is eliminated. TIPS provides a survival advantage over large volume paracentesis in patients with refractory ascites, especially in patients who are young and who have relatively normal liver function (Figure 2).

Liver transplantation should always remain a treatment option in patients with refractory ascites (Figure 3).
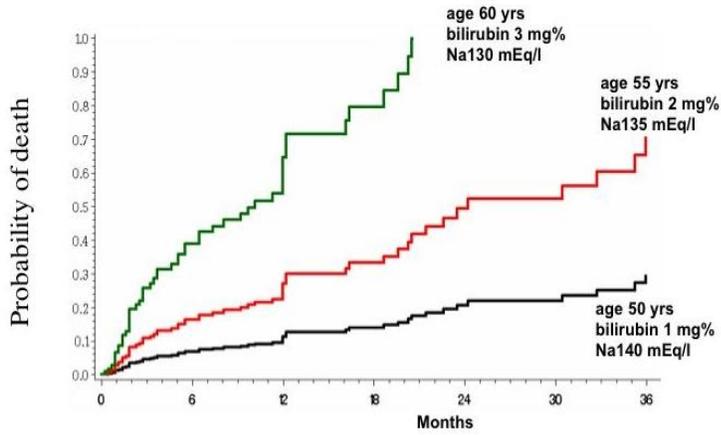
Figure 3. Survival of patients according to patient characteristics following the insertion of a transjugular intrahepatic portosystemic stent shunt for treatment of refractory ascites.

Cirrhosis
&
Ascites

Serum ascetic fluid albumin gradient > 11 g/L
Exclude SBP

Sodium restriction to 44 – 66 mmoL/day
+
Stepwise increase of combination diuretics

Monitor daily weight
Monitor electrolytes and serum creatinine
Twice/week
Frequent 24 hour urine collections to
monitorcompliance and response

Refractory ascites

Large volume paracentesis   TIPS in the suitable patients

Consider liver transplantation

Figure 3. Management of ascites

2. Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is a common and often fatal complication of cirrhosis. It is a condition in which the ascites becomes infected in the absence of a recognisable cause of peritonitis (other than cirrhosis itself). The yearly risk of developing SBP after the onset of ascites is approximately 20-30%. Risk factors include a prior episode of SBP, recent esophageal variceal hemorrhage, an ascitic fluid protein of less than 10g/L and jaundice (bilirubin >43μmol/L). Curiously, in most cases, the infection occurs after the patient's admission into hospital. About one third of cases of SBP are asymptomatic, and the attending clinician should not hesitate in performing a diagnostic paracentesis in all persons admitted with ascites. The indications for diagnostic paracentesis to rule out a diagnosis of SBP are shown in Table 1.

Some patients with SBP may present with fever and/or abdominal pain. More often, the presentation is atypical, with worsening of hepatic encephalopathy or renal function. The "gold standard" for diagnosing SBP is an ascitic fluid PMN count of >250 cells/μL. A variant of SBP, known as culture-negative neutrocytic ascites are culture negative cases of suspected SBP with an ascitic fluid PMN count of >250 cells/μL. The patients with culture-negative neutrocytic ascites have the same clinical presentation, and carry the same unfavorable prognosis as those with SBP (Table 2). Positive culture results may take 48 hours, and Gram stains of ascitic fluid are only positive in 10-50% of infected patients. Therefore, treatment for suspected SBP should start immediately after the diagnostic PMN count, rather than waiting for positive culture results.

Another variant of SBP is monomicrobial non-neutrocytic bacterascites. In this scenario, the ascitic PMN count is <250 cell/μL, but the subsequent ascitic culture is positive. It is not known if this represents an early stage of SBP. It is recommended that the patient undergoes repeat paracentesis. If either the ascitic culture is again positive or the PMN count is >250 cells/μL, then the patient should be treated as having presumed SBP.

Gram negative bacilli account for 70% of cases of SBP. *E. coli* is the commonest pathogen isolated (Table 6). Anaerobic organisms are uncommon causes of SBP, as the oxygen tension in the ascitic fluid is too high for their survival. Among these, Bacteroides species appear to be more common than other anaerobes. A management algorithm for SBP is shown in Figure 4 Cefotaxime, a broad-spectrum third generation cephalosporin, is the treatment of choice for SBP. Its spectrum includes most organisms responsible for SBP, and it is not nephrotoxic when dosed in the usual therapeutic range. A five-day course of Cefotaxime 2 g intravenously every 8-12 hours is effective as a ten-day course.

Table 6. Micro-organisms that can cause spontaneous bacterial peritonitis

Gram negative bacilli	Gram positive organisms	Anaerobes
E. coli	Streptococcus	Bacteroides
Klebsiella	Group D Streptococcus	Clostridia
C. freundii	S. pneumoniae	Lactobacillus
Proteus	S. aureus	
Enterobacter		

Cirrhosis and ascites with
abdominal pain, fever,
new-onset encephalopathy
new-onset renal impairment

diagnostic paracentesis

↓

polymorphonuclear count >250/μL

+/-

positive ascitic fluid culture

IV cefotaxime 2gm every 8 –12 hours
Albumin infusion for patients with serum
creatinine >88.4μmol/L & bilirubin
>68.4μmol/L

↓

Repeat diagnostic paracentesis in 48 hours

Response   No response

Secondary prophylaxis   Search for causes of secondary SBP
(ciprofloxacin 750mg weekly
or norfloxacin 400mg daily)

↓

Consider liver transplantation

Figure 5. Management of spontaneous bacterial peritonitis

Other treatment options for SBP include intravenous followed by oral amoxicillin/clavulanic acid, or intravenous ciprofloxacin followed by oral treatment, or oral cipris in patients without septic shock, encephalopathy, azotemia, gastrointestinal bleed or ileus. These options explore the possibility of giving part of the treatment course as outpatients, thereby shortening the duration of hospital stay. However, monitoring patient compliance becomes mandatory if this course of action is to be followed.

Aminoglycosides should not be used for the treatment of SBP, since cirrhotic patients are particularly sensitive to their nephrotoxic effects and monitoring serum aminoglycosides levels is no guarantee against aminoglycoside induced nephrotoxicity. One study has shown that the

concomitant use of albumin can reduce the risk of renal impairment in these patients. However, further studies have shown that only patients with a baseline serum creatinine of >88.4 μmol/L and serum bilirubin >68.4 μmol/L will require albumin infusion for protection from renal failure, as the risk for the development of renal failure is very low in patients with serum creatinine and bilirubin levels below these cut-off values.

The response to treatment should be assessed by both evaluating the symptoms and signs of infection, and performing at least one follow-up paracentesis after 48 hours of antibiotic therapy. Clinical improvement should parallel a fall in the ascitic PMN count. A reduction of less than 25% in relation to the pre-treatment value is often considered to represent failure of antibiotic treatment.

Secondary bacterial peritonitis should be considered if the following features are present: (i) poor clinical response to antibiotic therapy; (ii) multiple organisms grown from the ascitic fluid; (iii) ascitic fluid protein concentration >l0 g/L or ascitic glucose <3 mmol/L; (iv) PMN count remains high despite antibiotic therapy. If secondary bacterial peritonitis is suspected, antibiotic coverage should be broadened with the addition of metronidazole and ampicillin. Radiographic examinations are required to exclude perforation of the gastrointestinal tract, with emergency surgery only where gut perforation is confirmed.

Despite successful treatment of SBP, the prognosis of these patients remains poor. The one-year mortality probability of SBP recurrence is 40-70% in patients who have had previous episodes of SBP. Routine selective intestinal decontamination with oral non-absorbable antibiotics has proved to be effective in reducing recurrence. Norfloxacin 400 mg daily, Trimethoprim/sulfamethoxazole 160/800mg daily, or Ciprofloxacin 750 mg weekly are the drugs of choice, as they rarely cause bacterial resistance and have a low incidence of side effects when administered chronically. Trimethoprim/sulfamethoxazole 160/800mg daily may confer greater gram-positive coverage. Cirrhotic patients with upper gastrointestinal bleeding are at a high risk for developing severe bacterial infections, including SBP, within the first days of the hemorrhagic episode. Antibiotic prophylaxis is effective in improving survival in cirrhotic patients with gastrointestinal hemorrhage. Thus, antibiotic prophylaxis is recommended in all cirrhotic patients who have a GI bleeding. The optimal dose and the duration of treatment in this setting have not yet been established. There is no evidence to support routine primary prophylaxis of all ascitic patients against SBP, and indiscriminant use of antibiotics in cirrhosis may lead to the development of antibiotic resistance. However, in certain settings such as patients with significant jaundice or low protein ascites, it may be prudent to consider primary SBP prophylaxis.

A recent meta-analysis has demonstrated that the use of non-selective beta-blockers can retard bacterial translocation across the bowel wall, and therefore can reduce the risk for SBP in patients with ascites. Although not widely available, the detection of bacterial DNA in ascitic fluid without the occurrence of SBP has been shown to be associated with decreased survival. There are no studies to date to determine whether these patients require antibiotic prophylaxis. Despite decreased SBP recurrence rates with prophylactic antibiotics, no change in mortality has yet been demonstrated.

All patients who have experienced one episode of SBP should be considered for liver transplantation.

Chapter 28: Hepatorenal Syndrome
S. E. Congly and A. I. Aspinall

1. Definition

Hepatorenal syndrome (HRS) was first described in 1994 by the International Ascites Club as a specific form of renal insufficiency (RI) associated with end stage liver disease (ESLD), occurring in the absence of another cause of acute kidney injury (AKI) (Salerno, Gut, 2007; Gines 2009, Gines 2010, Runyon 2009).

The 2010 International Ascites Club revised criteria for diagnosing HRS are presented in Table 1. In a cirrhotic patient with ascites and HRS, a doubling of creatinine within two weeks has been proposed to be diagnostic of Type 1 (rapidly progressive) HRS. Prognosis is poor in patients with HRS. The overall median survival is approximately 3 months, and in those with a high Model for End-stage Liver Disease (MELD) score and Type 1 HRS, there is a median survival of approximately only 1 month. Type 1 HRS is rapidly progressive and often develops after an inciting event (such as spontaneous bacterial peritonitis [SBP] or an esophageal variceal hemorrhage). Type 1 HRS can also develop in the absence of a clear precipitant. Type 2 HRS also develops in the presence of ascites and is characterized by a slow but progressive deterioration in renal function. In such patients, a precipitating event such as SBP may result in the development of Type 1 HRS.

Table 1: International Ascites Club 2007 Diagnostic Criteria for HRS (Salerno 2007)

- o Cirrhosis with ascites.
- o Serum creatinine >133 μmol/l (1.5 mg/dl).
- o No improvement of serum creatinine (decrease to a level of ≤133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- o Absence of shock.
- o No current or recent treatment with nephrotoxic drugs.
- o Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

2. Pathogenesis

There is derangement of cardiovascular and neuroendocrine function in HRS and several factors have been proposed to be important in the development of HRS. The splanchnic arterial vasodilation that results from severe portal hypertension is a key initiating event. This results in a decrease in peripheral effective arterial volume and a decrease in mean arterial pressure (MAP). In turn there is activation of the systemic renin-angiotensin-aldosterone system (RAAS), subsequent renal arterial vasoconstriction, and greater sensitivity of renal perfusion to small changes in MAP. Cirrhotic cardiomyopathy results in an inappropriately low compensatory increase in cardiac output, further compromising renal perfusion. A number of soluble circulating vasoactive mediators have also been implicated in decreasing renal perfusion and the glomerular microcirculation.

3. Differential Diagnosis and Evaluation of Acute Kidney Injury

Apart from HRS, cirrhotics are at increased risk of Acute Kidney Injury (AKI) for a variety of reasons. Hypovolemia due to excessive diuresis, gastrointestinal (GI) hemorrhage, or other GI losses (such as excessive lactulose administration or diarrheal illness) can produce a clinical picture similar to HRS. Parenchymal kidney disease can result from many different

causes, including diabetic or hypertensive nephropathy, glomerulonephropathies associated with chronic viral hepatitis, and nephrotoxic medications (such as NSAIDs or aminoglycosides). An active urine sediment characteristic of parenchymal kidney disease can help discriminate these etiologies from HRS. A renal biopsy is occasionally required to discriminate between causes of parenchymal kidney disease. Contrast dyes, used in abdominal CT imaging and angiography, can also precipitate AKI. Acute tubular necrosis (ATN) can result from both long-standing HRS and pre-renal AKI and ATN is suggested by the presence of granular casts (epithelial cells) on urinalysis. A fractional excretion of sodium <1% suggests intact tubular function (and thus the absence of ATN).

In cirrhotic patients with AKI, thorough investigations are warranted to determine the cause of AKI and the etiology of any precipitant of HRS. An assessment of liver function and investigations to rule in or out the presence of sepsis are indicated. Urine microscopy and studies for electrolytes and protein can help rule in or out parenchymal renal disease. A renal ultrasound helps rule out obstructive etiologies of renal failure. Daily serum electrolytes and creatinine help follow responses to therapy and to screen for the development serious electrolyte disturbances (such as severe hyponatremia and hyperkalemia).

4. Treatment and Outcomes

As the mechanism of HRS is peripheral vasodilation resulting in renal arterial vasoconstriction (see "Pathogenesis" above), current therapies for HRS include administration of agents that cause alpha-adrenergic receptor-mediated vasoconstriction, and those that increase the effective arterial volume, thereby promoting renal perfusion. Collectively, such therapy is associated with improved short term survival and reversal of HRS in 52% of patients (Gluud 2010). Treatment with agents thought to be directly vasodilatory for the renal arterial supply (such as non-pressor doses of dopamine) are ineffective (Angeli 1999).

Terlipressin, which is not currently available in North America, is the most comprehensively studied pressor (Table 2). In randomized controlled trials (RCT), terlipressin usually has been co-administered with albumin. Contraindications to terlipressin include ischemic cardiovascular disease, and patients should be observed for the development of ischemic heart disease, arrhythmias, mesenteric and digital ischemia and volume overload. Patients usually are treated for up to 14 days.

Two small studies have shown a role for midodrine in treating HRS when used in combination with octreotide and albumin (Angeli 1999, Wong 2004), and a single small uncontrolled trial with norephinephrine also showed efficacy (Duvoux 2002). Collectively, a meta-analysis of randomized studies using pressor agents in HRS (Gluud 2010) has shown a significant decrease in all cause mortality (RR 0.82, CI 0.70-0.95), improvement in renal function (RR 2.00, CI 1.11-3.62) and resolution of HRS (RR 3.76, CI 2.21-6.39).

Non-pharmacologic therapy using transjugular intrahepatic portosystemic shunts (TIPS) has been studied in HRS in small uncontrolled trials. TIPSS insertion has been successful in normalizing renal function in some HRS Type 1 patients first treated with midodrine (Wong, Hepatology, 2004). Renal function has also been shown to improve in a small uncontrolled trial of seven patients treated with TIPSS as primary therapy for HRS (Guevara 1998). Intermittent hemodialysis (IHD) is not associated with any significant survival improvement in patients with HRS and is often inadequate and limited by hypotension during the dialysis run. However, IHD is sometimes viewed as a bridge to liver transplantation (LT) and reserved for those patients who are LT candidates.

Table 2: Pharmacological Treatment of HRS

Treatment	Level of evidence	Dose	Outcomes
o Terlipressin (with Albumin)	o Randomized and non-randomized controlled trials	o 0.5-1.0 mg i.v. bolus q4-6h, increased to 2.0 mg i.v. q4-6h after 3 days of therapy if Cr has not decreased by at least 25%	o Renal function improved in 40-50% of patients and improved 30 day survival
o Octreotide/ Midodrine (with Albumin)	o Non-randomized controlled trial/Case series	o Octreotide 100-200 ug s.c. t.i.d. Midodrine 7.5-12.5 mg po t.i.d.	o Renal function improved and improved 30 day survival
o Norepinephrine (with Albumin)	o Case Series	o 0.5-3.0 mg/hr i.v.	o HRS Type 1 reversed in 10/12 patients
o Albumin	o Randomized and non-randomized controlled trials	o Various doses (ie 1 g/kg i.v. day 1 followed by 20-40g i.v. daily)	

Abbreviations: Cr, serum creatinine

LT is well recognized to reverse HRS. When ATN complicates longstanding HRS in LT candidates, resulting in irreversible RI, combined LT and kidney transplantation can be considered, and criteria have been proposed to identify those who may benefit from combined transplantation (Gines 2009).

Measures can be taken to minimize the evolution of HRS in cirrhotics with ascites. The administration of albumin in patients with SBP reduces the evolution of HRS (Salerno 2007), and the use of pentoxyphylline dose in severe alcoholic hepatitis may also reduce the development of HRS (Gines 2010).

5. Careful and Appropriate Treatment of Ascites and SBP

The prognosis for cirrhotic patients with AKI is poor with an overall survival of 52% at one month and 20% at six months. Mortality is higher with Type 1 HRS than Type 2 with median survivals of one month and six months respectively. RI prior to LT is independently associated with a greater frequency of RI after LT (Ojo 2003).

6. Summary

AKI is a common and severe complication in decompensated cirrhotic patients. There are multiple possible causes of AKI in these patients, and HRS in particular is associated with poor survival in the absence of LT. Pharmacologic and non-pharmacologic therapy is effective in treating HRS in some patients. First line therapy for HRS Type 1 is the administration of vasoconstrictors with albumin.

534
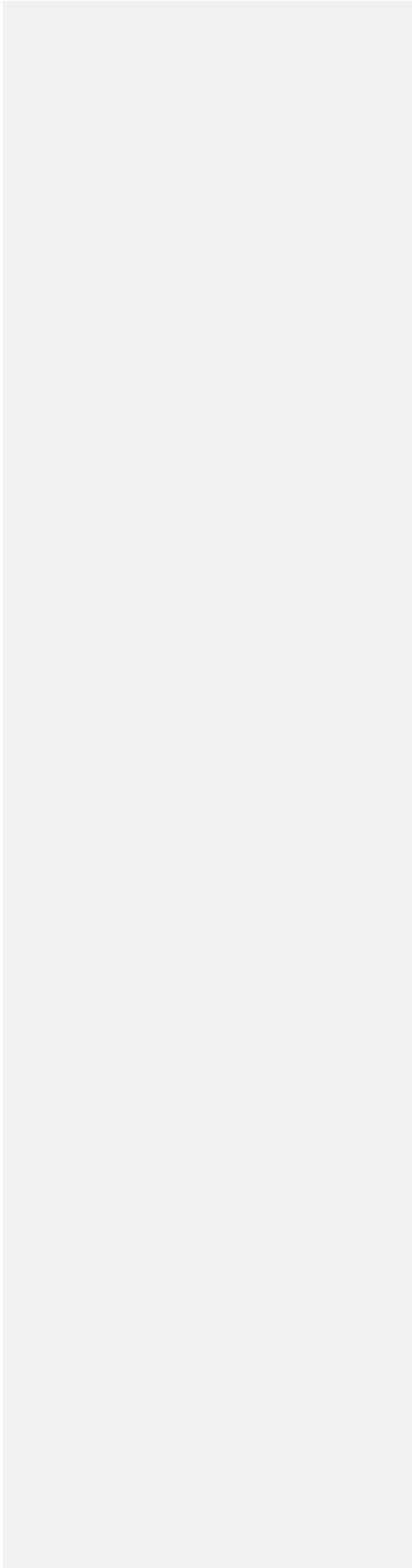
Chapter 29: Hepatatic Encephalopathy
J. Leonard

1. Definition

Hepatic encephalopathy (HE), also known as portosystemic encephalopathy, is a complex, potentially reversible neuropsychiatric syndrome that occurs as a consequence of acute or chronic liver failure, and is associated with excessive neuro-inhibitory neurotransmission.

2. Clinical Presentation

Patients with this condition will present in a variety of ways (Table 1). Usually there will be a history of chronic liver disease. Occasionally this will be the first sign of an acute liver problem. Patients with chronic disease often have other manifestations of their liver disease including jaundice, ascites and gastrointestinal bleeding. Occasionally HE is the only apparent manifestation of decompensated liver disease. The usual physical signs and laboratory abnormalities associated with advanced liver disease may be present. These physical findings include muscle wasting, jaundice, peripheral edema, and ascites. Occasionally fetor hepaticus, a sickly-sweet smell from the mercaptanes in the breath, will be present. In some cases HE accompanies acute, fulminant hepatic failure. In those cases the physical signs of chronic liver disease will be absent. Typical laboratory abnormalities of both acute and chronic disease include an elevated INR, elevated bilirubin and possibly low albumin concentration. Hypoglycemia may be seen, but this is typically a late finding.

Table 1. Clinical Presentation of HE

➢ Acute Liver Failure

➢ Chronic Liver Disease
  o   With decompensation (Jaundice, ascites, esophageal varices)
  o   No symptoms (mHE)
  o   Symptoms (West Haven Criteria: Table 2)

➢ Refractory HE
  o   Dementia, spastic paresis, cerebellar degeneration, extrapyramidal movement disorders

The clinical picture of HE can be quite variable, representing a continuous spectrum of disease, from subtle disturbances in the sleep-wake cycle to overt coma. Hepatic encephalopathy is characterized by changes in personality, consciousness, behavior and neuromuscular function. The most commonly used grading system is the West Haven Criteria (Table 2).

Table 2. West Haven Criteria for Hepatic Encephalopathy

Stage	Consciousness	Intellect and Behaviour	Neurological findings
0	- Normal	- Normal	- Normal exam
1	- Mild lack of awareness	- Shortened attention span Impaired attention or subtraction	- Mild asterixis or tremor
2	- Lethargic	- Disoriented - Inappropriate behavior	- Obvious asterixis - Slurred speech
3	- Somnolent but arousable	- Gross disorientation - Bizarre behaviour	- Muscular rigidity and clonus - Hyperreflexia
4	- Coma	- Coma	- Decerebrate posturing

HE may be present in up to 80% of patients with cirrhosis and accounts for a significant proportion of admissions to hospital. The earliest feature is often reversal of the diurnal sleep pattern or subtle personality changes and irritability. This can progress to include apathy, hypersomnia, and personal neglect. Later stages include delirium and even coma. Neurologic signs may include hyperreflexia, rigidity, and myoclonus. Asterixis (asymmetric flapping motions of the outstretched, dorsiflexed hands) can be easily checked in a routine clinical exam. It may be present in HE, but is not diagnostic as it may occur in other causes of metabolic encephalopathy.

Hepatic encephalopathy associated with acute liver failure has a rapid onset and progression. It is usually complicated with cerebral edema, which can lead to seizures and lateralizing neurologic signs. HE associated with chronic liver disease may present acutely, but may also present gradually with slow progression of symptoms. Occasionally, a refractory pattern emerges leading to debilitating syndromes such as dementia, spastic paresis, cerebellar degeneration and extrapyramidal movement disorders.

When approaching a patient with severe liver disease who has an altered level of consciousness or other neurological features, it is important to rule out other causes of changes in mental status and neurologic disease. This includes exclusion of central nervous system disease such as subdural hematoma, tumor, or CVA, as well as CNS infection and drug ingestion. One may need to distinguish the neurologic changes commonly seen in patients with alcoholic liver disease and Wilson disease.

3. Theories of Pathogenesis

The syndrome of HE is not a single clinical entity. It may reflect either a reversible metabolic encephalopathy, brain atrophy, brain edema or any combination of these conditions. The mechanisms of brain dysfunction in liver failure are not clearly known (Table 3). In advanced HE, the effects of brain swelling, impaired cerebral perfusion and abnormalities in neurotransmitter systems cannot be distinguished. Factors of importance in the pathogenesis of HE are the shunting of portal venous blood around the liver into the systemic circulation and the presence of hepatocellular dysfunction. Encephalopathy probably results from a number of mechanisms that include, in part, one or more toxic products that originate in the gut that are usually metabolized by the liver entering the systemic circulation and reaching the brain.

Table 3. Theories of Pathogenesis of HE

- ↑ NH_3
  - GUT: urease bacteria, ↑glutaminase activity* (Increased glutamate, NH3 and free radicals
  - Liver: ↓ urea cycle metabolism by hepatocytes, ↑ shunting to systemic circulation
  - Muscle: atrophy leads to less NH_3 metabolism by urea cycle
  - Kidney: ↑ renal production in presence of hypokalemia and metabolic alkalosis
  - Brain: ↑ BBB permeability to NH_3 and glutamate; astrocyte edema, neuro-inhibition
- ↑ Endogenous benzodiazepine-like substances, ↑ GABA-ergic transmission
- ↑ Neurotoxic SCFAs, phenols, mercaptanes
- ↑ NH_3 toxicity
- ↑ SCFAs and AAA + ↓ BCAA
- ↑ False neurotransmitters, ↓ neuro-excitatory neurotransmission (glutamine, catecholamines)
- ↑ Neuro-inhibitory neurotransmitters (GABA, gabba-aminobutyric acid; AAA, aromatic amino acids; BCAA, branched chain amino acid

$$\text{Glutamine} \quad \underset{\text{Glutamine synthetase}}{\overset{\text{Glutaminase* (deamidation)}}{\rightleftharpoons}} \quad \text{Glutamate} + NH_3 + FR$$
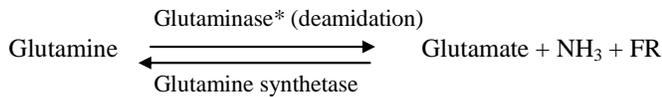
Abbreviation: AAA, aromatic amino acid; BCAA, branched chain amino acid; FR, free radicals; NH3, ammonia

Abnormalities of ammonia metabolism are most frequently implicated in the pathophysiology of HE. The normal gut flora produce a urease enzyme that enzymatically cleaves NH3 from protein in the lumen. Ammonia derived from colonic bacteria and from deamination of dietary glutamine in the small bowel is absorbed into the portal circulation. The intact liver clears almost all of portal vein ammonia, converting it to glutamine and preventing its entry into the systemic circulation. In severe liver disease, ammonia reaches the systemic circulation because of spontaneously created vascular shunts within and around the hepatocytes and the inability of the liver to metabolize the ammonia. Increased blood-brain barrier permeability likely facilitates the entrance of ammonia and other toxic metabolites into the brain. This contributes to astrocyte swelling and edema.

Alternative proposals of gut-derived toxins include endogenously produced benzodiazepine-like substances which activate GABA-ergic transmission, as well as neurotoxic short-chain fatty acids, phenols and mercaptanes which may potentiate ammonia toxicity. Another hypothesis proposes that increased levels of short-chain fatty acids and aromatic amino acids associated with decreased levels of branched-chain amino acids cause production of false neurotransmitters. As well, the principle neuro-inhibitory neurotransmitter γ- aminobutyric acid (GABA) is increased in encephalopathy. False neurotransmitters, including an endogenous modulator of GABA receptors, suggest involvement of the GABA-diazepam receptor complex in the pathogenesis of HE. Thus, the synergistic action of ammonia with other toxins likely accounts for many of the abnormalities occurring in liver failure, such as the changes in blood-to-brain transport of neurotransmitter precursors, the metabolism of amino acid neurotransmitters and cerebral glucose oxidation. These changes may lead to activation of inhibitory (GABA, serotonin) and impairment of excitatory (glutamine, catecholamines) neurotransmitter systems, resulting in enhanced neural inhibition and HE.

4. Diagnosis

There is no specific diagnostic test for HE. It is usually based on the clinical impression, but this sometimes makes a definite diagnosis difficult. The history and the clinical examination, including a complete mental status and neurologic examination, are the most important tools for diagnosing HE. HE also needs to be accurately distinguished from other causes of neurologic disease and encephalopathy.

The presence of asterixis is helpful but not pathognomonic for HE. It can also be seen in carbon dioxide intoxication and uremia. It is usually tested when the patient is sitting erect with outstretched hands. A flapping tremor can then be seen. If the patient is unable to sit forward, then gripping the examiner's hand could elicit the same oscillatory movement. Upon examination of the motor system, focal deficits are typically not seen, and should prompt further investigations to search for an alternate diagnosis such as intracranial bleeding or an ischemic event.

Imaging with either CT or MRI is usually necessary in these cases. Blood tests help verify the presence and severity of liver disease, and rule out other causes of encephalopathy such as renal failure, hypoxia, CO_2 retention and drug overdose. Blood tests are also helpful in identifying precipitating factors of HE such as hypoglycemia, azotemia, electrolyte imbalance (hypokalemia and hypnatremia) and infection. An elevated serum ammonia (NH3) concentration is often observed, but correlates poorly with the degree of encephalopathy and may be normal in up to 10% of cases with HE. It is not useful to follow the serum NH3 concentration once a diagnosis of HE has been made. Trends of the NH3 level over time do not correlate with response to therapy, and degree of elevation of NH3 does not correlate with the severity of HE.

Lumbar puncture is usually not necessary but in certain situations may be required to rule out other CNS pathology. In HE the cerebrospinal fluid is usually normal, or may show increased protein and increased GABA levels. The EEG shows slow, triphasic wave activity mainly over the frontal areas. Although this pattern is highly sensitive and characteristic of HE, it is not specific for this condition.

In patients with clinical symptoms of HE, neuropsychiatric testing is not necessary. It may be helpful in establishing the diagnosis of mild HE where the diagnosis is not clear. A Psychometric Hepatic Encephalopathy Score (PHES) includes a battery of five paper-pencil tests including the line tracing test, digit symbol test, serial dot test and two number connection tests. The psychometric tests are particularily useful to diagnose minimal hepatic encephalopathy (mHE). It is important to make the diagnosis of mHE since these persons with chronic liver disease have an increased risk of having motor vehicle accidents, and then driving priviledges may need to be restricted.

5. Management

HE occurring in acute liver failure is usually accompanied by cerebral edema, and carries with it a poor prognosis. Unless the liver shows signs of spontaneous recovery, these patients should be considered for urgent orthotopic liver transplantation. Patients with grade 3 or 4 HE should be managed in intensive care, as there is often associated multi-organ failure. Management may include elective ventilation, mannitol infusion and intracranial pressure monitoring.

Provision of meticulous medical and nursing care to these confused and often comatose patients is very important for their recovery, and to avoid potential complications.

Most HE occurs in patients with chronic liver disease and is due to a clinically apparent precipitating event or the development of a portosystemic shunt, either spontaneously or surgically created (Table 4). The most important aspect of management is the prompt recognition and treatment of these precipitating factors (Figure 1). Exogenous factors include markedly increased dietary protein, constipation, administration of certain drugs (especially sedatives or narcotics), gastrointestinal bleeding, azotemia, hypoxia and infection (urinary, respiratory, spontaneous bacterial peritonitis). Development of underlying hepatocellular carcinoma may present as worsening HE. Dehydration, hyponatremia, hypokalemia and alkalosis (often the result of diuretic therapy) should be corrected. Correction of it is essential as hypokalemia increases renal ammonia production.
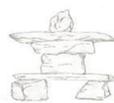
Table 4. Common precipitants of hepatic encephalopathy in chronic liver disease

- Increased ammonia production or absorption
  - Excessive dietary protein
  - Gastrointestinal bleeding
  - Electrolyte disturbance (hypokalemia)
  - Zinc deficiency
  - Metabolic alkalosis
  - Constipation
  - Azotemia

- Infection
  - Spontaneous bacterial peritonitis (SBP)
  - Urinary tract infection
  - Pulmonary

- Dehydration
  - Vomiting
  - Diarrhea (spontaneous, or due to laxative use)
  - Diuretics
  - Large volume paracentesis

- Drugs
  - Narcotics, sedatives
  - Alcohol

- Portosystemic shunting
  - Transjugular intrahepatic portosystemic shunt (TIPS)
  - Surgical shunts
  - Spontaneous shunts

- Vascular Occlusion
  - Portal vein thrombosis
  - Hepatic vein thrombosis

- Additional Liver Disease
  - Hepatocellular Carcinoma
  - Superimposed liver injury (acute hepatitis, drug-induced liver injury)

- Noncompliance with medical treatment

- Surgery

In conjunction with treating the potential triggering events, the next goal of therapy is to lower the level of neurotoxic substances by emptying nitrogenous wastes from the gut. Restricting dietary protein has never been shown to be effective in treating HE. Often these patients have already lost significant muscle mass, and restricting dietary protein only worsens this problem.

Constipation can be avoided by the use of laxatives. A commonly used laxative is lactulose, a synthetic disaccharide that is degraded by intestinal bacteria into lactate and acetate to produce stool acidification and an osmotic diarrhea. The acidification of colonic contents reduces ammonia absorption in part by trapping nitrogenous compounds in the lumen ($NH_3 + H^+ \rightarrow NH_4$). The daily dose of lactulose should be titrated to produce two to four soft, acidic (pH<6.0) stools per day. For most patients, this will be between 15-30 cc orally once to four times per day. Patients in coma or with small bowel ileus can receive lactulose by enema. Patients will often complain of an excessively sweet taste, flatulence, diarrhea and cramping as the most common side effects. Lactitol can be used instead of lactulose. Overdosing can lead to excessive diarrhea, which can result in fluid and electrolyte depletion. The resultant renal failure can worsen HE. Lactulose can be used chronically to reduce the frequency of episodes of HE. Patients should be instructed to adjust their dose based on their stool output. Although lactulose is considered by most to be the mainstay of therapy, randomized controlled studies proving the efficacy are lacking.

Alternatively, antibiotics such as neomycin and metronidazole may be used. These inhibit urea-splitting and deaminating bacteria, thereby reducing the production of ammonia and other potential toxins. Neomycin use is now limited due to its potential nephrotoxic and ototoxic side-effects. Because of the potential toxicity, long-term use of these antibiotics is not recommended. Limited date support a short course of the combined use of lactulose and antibiotics in selected resistant cases.

Rifaximin is a nonsystemic antibiotic, and is better tolerated with fewer side effects and complications than lactulose. It has been approved for use in the United States but not in Canada. It appears to be effective for the treatment of both acute episodes and maintenance therapy.

When HE becomes refractory, nutritional support with formulas rich in branched chain amino acids (BCAA) but low in aromatic amino acids has been suggested (on the basis of increased aromatic amino acids and decreased BCAA found in HE and their effect on neurotransmitter synthesis). Most studies with oral BCAA have shown clinical improvement of mild HE, with increased protein tolerance. In contrast, studies with IV BCAA have been inconclusive. Intravenous ornithine aspartate has been proven helpful, and the efficacy of the oral form is being tested in controlled trials.

Two of the five enzymes involved in the metabolism of ammonia to urea are zinc dependent. There is a significant incidence of zinc deficiency in cirrhosis, and some studies have shown improvement of HE with zinc replacement. Therefore, zinc deficiency should be sought and corrected if present.

Decreased dopaminergic neurotransmission activity has also been suggested to play a role in HE. However, controlled trials failed to demonstrate a beneficial effect of levodopa or bromocriptine treatment. Also, increased benzodiazepine receptors have been suggested to play a role in HE, but in controlled trials, benzodiazepine receptor antagonists such as flumazenil showed only modest success. Unfortunately, both bromocriptine and flumazenil can potentially

decrease the seizure threshold, and because of this and their questionable efficacy, they are typically no longer used.

Other therapies being explored include the use of probiotics to modify enteric bacteria population, and the use of sodium benzoate to help eliminate ammonia from the body.

HE as a complication of spontaneous or surgically created portosystemic anastamoses or transjugular intrahepatic shunts (TIPS) is usually managed successfully with conventional therapy. Refractory HE complicating TIPS can be helped by implanting a reducing stent to reduce blood flow through the TIPS. Orthotopic liver transplantation has the potential to entirely reverse HE. Thus, this procedure should be considered in all patients with HE whose liver disease makes them suitable for liver transplantation.

Possible HE – perform complete history and physical exam

Diagnosis confirmed

diagnosis not confirmed – pursue other potential diagnosis

Presence of precipitating factor

Yes

No

Treatment aimed at

Underlying cause and HE

empiric treatment of HE

Lactulose or Rifaxamin
(ICU admission if ≥Grade 3)

Good Response

Poor response

Continue

add metronidazole ± zinc
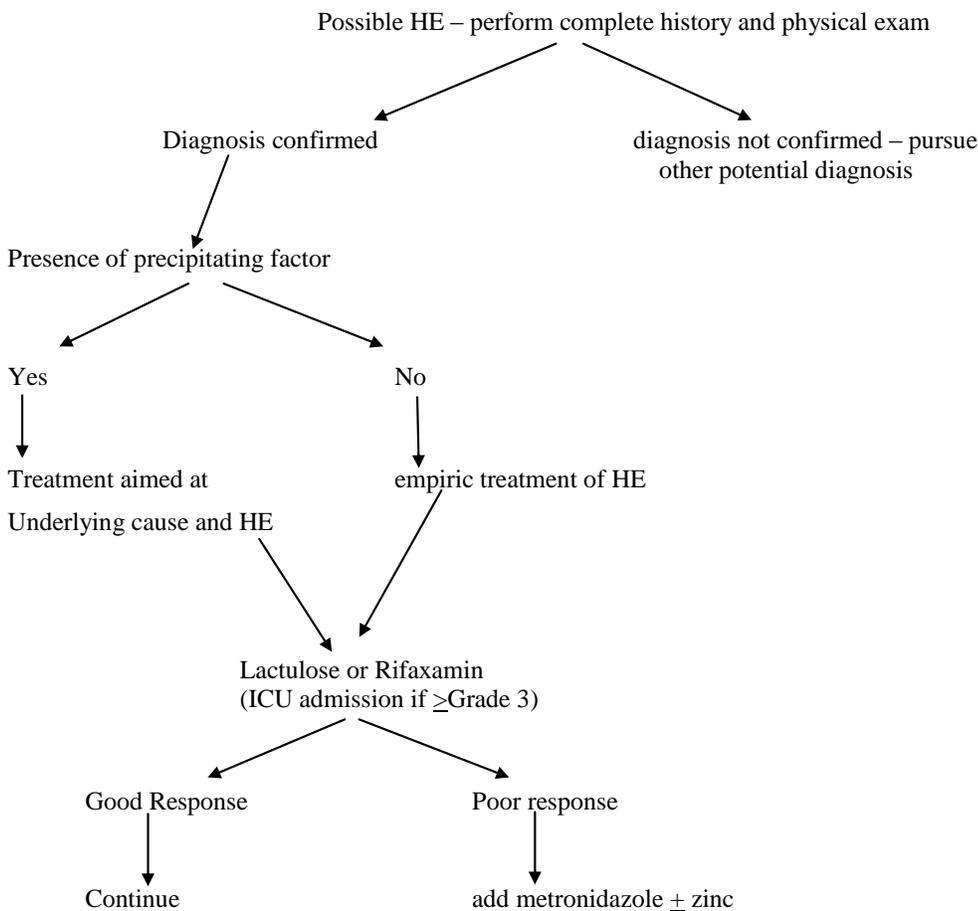
Figure 1. Suggested management of Hepatic Encephalopathy (HE)

Chapter 30: Liver Transplantation

E. L. Renner, L. B. Lilly and G. A. Levy

1. Introduction

Starzl performed the first human liver transplant in 1963 in a 3-year-old boy with biliary atresia. The first successful liver transplant was not performed until 1967, when a one and a half year old girl with hepatocellular carcinoma was transplanted. Unfortunately, she died of recurrent tumour at 17 months. One-year-survival in the early years was 25 to 35%, using methylprednisilone and azathioprine as immunosuppression. However, with the introduction of cyclosporine in the early 1980s, liver transplantation became a clinical reality, and now offers one and five year survival rates of 80-90% and 70-80%, respectively. With the dramatic improvement in results, liver transplantation became recognized as the definitive management for end stages of acute and chronic liver diseases.

The number of liver transplant centres in North America has proliferated to more than 100, and more than 6,000 liver transplants are performed yearly in the United States alone. In Canada, there are active centres in Halifax, NS; Montreal, PQ; Toronto and London, ON; Edmonton, AB and Vancouver, BC. Around 400 liver transplants are performed yearly in Canada. The rate-limiting step in the application of transplantation to persons with liver disease has become donor availability.

2. Assessment for Transplantation

A person should be considered for liver transplantation when three conditions are met: 1) the diagnosis of irreversible acute or chronic liver failure is made, from which the anticipated survival is clearly inferior to that of transplantation; 2) no alternative medical or surgical therapy exists (such as TIPS for recurrent portal hypertensive bleeding or refractory ascites); and 3) no absolute contraindications or significant comorbidities are present that might significantly raise the risk of transplantation and compromise long-term outcome. In most patients with chronic liver disease, it is decompensation, i.e. the development of complications of portal hypertension (ascites, encephalopathy or variceal hemorrhage) and/or of liver dysfunction (jaundice) that prompts referral for transplantation.

The most common indications for liver transplantation in adults and children are shown in Table 1. End-stage liver disease due to hepatitis C remains the most common indication in adults, comprising around 40% of patients on the waiting list. In most programs, patients with alcoholic liver disease make up a further 15-20%, with non-alcoholic steatohepatitis (NASH) and hepatitis B contributing each approximately 5-10%. Cholestatic liver diseases (Primary Biliary cirrhosis, Primary sclerosing cholangitis; 10-15%) and cirrhosis attributable to hemochromatosis, alpha-1-antitrypsin deficiency or autoimmune hepatitis, in addition to occasional patients with polycystic liver disease and other unusual indications, make up the remainder. Most programs perform fewer than 5% of their transplants for persons with fulminant liver failure.

Table 1. Liver transplantation: indications

➤ End-stage chronic liver disease
Cirrhosis related to viral hepatitis
- ○ HBV ± HDV (HBV-DNA below detection limit)
- ○ HCV

➤ Alcoholic cirrhosis
- ○ Cirrhosis related to non-alcoholic steatohepatitis (NASH)

- Cholestatic liver disease
  - Primary biliary cirrhosis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Biliary atresia
  - Cholestatic sarcoidosis
  - Graft-vs-host disease
  - Chronic ductopenic rejection
  - Secondary sclerosing cholangitis

- Drug-induced cholestasis and secondary biliary cirrhosis

- Neoplasms
  - Hepatocellular carcinoma (HCC) within Milan criteria (see text)
  - Only exceptionally other liver tumors

(These include hepatoblastoma, fibrolamellar cancer, hemagiendiothelioma, and neuroendocrine tumors. Hilar cholangiocarcinoma is generally regarded as a contraindication for liver transplantation outside, of clinical trials)

- Fulminant hepatic failure
(drugs, viral hepatitis A–E, herpes, adenovirus, Wilson's disease, Reye's syndrome)

- Metabolic liver disease
(alpha-1-antitrypsin deficiency, Wilson's disease, hemochromatosis, glycogenosis type 4, tyrosinemia, Gaucher's disease, cystic fibrosis)

- Vascular disease
  - Budd-Chiari syndrome
  - veno-occlusive disease)

- Congenital
  - Caroli's disease, choledochal cyst, polycystic disease, hemangioma

---

The hepatitis C virus (HCV) universally (ie. 100%) infects the graft upon reperfusion of the liver at the time of transplantation. In 10-30% of patients, recurrent hepatitis C after liver transplantation runs an aggressive course, leading to graft cirrhosis, with associated morbidity and mortality in ≤5 years. Treatment-induced HCV clearance (sustained virological response) prior to liver transplantation prevents HCV recurrence post transplant. Unfortunately, the current standard therapy (pegylated interferon alpha and ribavirin) is suboptimally tolerated and effective in most decompensated HCV patients who are on the waiting list for transplantation. Nevertheless, antiviral therapy for HCV should be considered in selected cases.

Liver transplantation is not a therapy for alcohol dependence. Only selected patients with end-stage alcohol related liver disease, i.e. those who have proven to be compliant and able to stay away from alcohol, should be considered for transplantation. In most liver transplantation programs, a ≥6 months supervised abstinence period in the community, (i.e. with potential access

to alcohol), is required prior to listing for liver transplantation. The liver function of a sizable proportion of patients with end-stage alcoholic liver disease will recover during this minimum 6-month time period, thereby eliminating the need for transplantation. In addition, most centers will require some form of addiction counseling, including documentation that the patient understands and accepts that alcohol was the problem leading to his/her liver disease, and a stable psychosocial situation with an intact support network.

In parallel with the obesity epidemic, patients with NASH cirrhosis (or those classified as cryptogenic cirrhosis with a history or the presence of risk factors for NASH, such as diabetes or obesity) are increasingly referred for transplant assessment. Many of these patients have an increased perioperative and long-term cardiovascular risk that needs to be thoroughly addressed prior to listing.

Transplantation for hepatitis B (HBV) has become standard. While initial efforts were plagued by high recurrence rates of HBV and suboptimal patient survival due to the lack of effective antiviral therapy, current preventive strategies using perioperative anti-HBs immunoglobulin (HBIG) in combination with long-term nucleoside or nucleotide analogues such as lamivudine have almost eliminated HBV disease recurrence. Thus, patient and graft survival rates are today similar to those for other transplant indications. Most programs still require that patients have low levels of viral replication (either occurring spontaneously, or induced by antiviral therapy) prior to transplantation, in order to reduce the risk of recurrence, and thereby to improve outcome.

Hepatocellular carcinoma (HCC), particularly in patients with viral hepatitis, is an increasingly common indication for liver transplantation. In Toronto for example, 30-40% of patients transplanted in recent years had hepatomas. The best results (around 80% disease-free 5-year survival) have been described in patients fulfilling the so-called Milan criteria, i.e. a single HCC nodule ≤5cm in diameter, or maximally 3 HCC nodules each ≤3cm in diameter, in the absence of evidence of vascular invasion and extrahepatic spread. Recently, several programs have proposed to expand these Milan criteria by demonstrating reasonable outcomes with so called "extended Milan criteria," allowing for the transplantation of larger and/or more multifocal HCCs. Note that none of these extended criteria are generally accepted.

Physicians should be aware of their transplant centre's policy when considering patients for referral. The exclusion of patients with contraindications to liver transplantation (Table 2) allows the best use of scarce donor resources, while maximizing patient benefit. Given the scarcity of donor organs, selection of the patient and the timing of the transplantation require individual assessment. The patient with decompensated cirrhosis should not be moribund, since this increases the risk of transplantation to an unacceptable degree. On the other hand of course, the liver patient should not be in such a stable condition that she/he might be able to live an independent life in the absence of liver transplantation.

In general, liver transplantation carries a survival benefit only if the MELD score (Table 3) is ≥15 points. To allow for the time required for evaluation and decision making, the treating physician should consider patient referral for liver transplantation when a patient with cirrhosis (and without obvious contraindications, Table 2) decompensates. Decompensation is considered to have applied when the patient develops ascites, portal hypertensive bleed, encephalopathy or jaundice and has a MELD score above 11 points.

Table 2. Liver transplantation: contraindications

➢ Absolute
  o Sepsis outside the biliary tree
  o Extrahepatic malignancy
  o Advanced cardiopulmonary disease
  o Severe pulmonary hypertension (Pulmonary Artery pressure >40-60 mm of Hg)
  o HIV/AIDS
  o Active alcohol and/or substance abuse
  o Inability to accept the procedure, understand its nature, or cooperate in the
  o Medical care required following liver transplantation (including noncompliance and lack of psychosocial support)

➢ Relative
  o Chronic renal insufficiency (may require liver/kidney transplant)
  o Advanced Age
  o Vascular access problems (portal and superior mesenteric vein thrombosis, or prior hepatic shunt surgery)
  o Other significant extrahepatic disease(s)
  o Inadequate psychosocial support

Table 3. Three month mortality for potential liver transplant recipients based on Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) score

	MELD					CTP		
	<9	10-19	20-29	30-39	>40	<7-9	10-12	13-15
No.	124	1800	1098	295	120	318	2357	588
%Mortality	1.9	6.0	19.6	52.6	71.3	4.3	11.2	40.1

MELD Score = 9.57 x loge creatinine mg/dL + 3.78 x loge bilirubin mg/dL + 11.20 x log INR + 6.53
Table adapted from Wiesner et al. Gastroenterology 2003; 124:91-96

3. Preoperative Workup

The principles behind the liver transplant workup are 1) to definitively establish the etiology of the liver disease; 2) to ensure that the patient's liver disease is a sufficient indication for the procedure; and 3) to identify contraindications, i.e. to ensure that liver transplantation will translate into a survival benefit and an acceptable long-term outcome for the patient. Given the scarcity of donor organs, a 50% 5-year survival is generally accepted as the threshold below which liver transplantation is regarded as futile. Assessment by a multidisciplinary team (which includes medical, surgical, anaesthetic, radiology, social and psychiatric specialists) is performed in all patients being considered for a liver transplantation, in order to ensure the success of the transplantation process.

4. Timing of Transplantation

Liver transplantation for end-stage chronic liver disease carries a survival benefit only if the recipient's MELD score (Table 3) is ≥15 points. In some liver transplantation centres, the MELD score may be adjusted upwards with MELD exception points (a modified MELD score), given for complications of end-stage liver disease that carry either a mortality or a drop out rate from the waiting list that is not adequately reflected by the non-modified MELD score. These MELD exception points might include presence of HCC or hepatopulmonary syndrome. Also, exceptional individual patients with MELD scores below 15 may warrant liver transplantation, for example the patient with Primary Sclerosing Cholangitis (PSC) and frequently recurring severe cholangitis episodes. Due to the scarcity of donor organs in most centers, poor quality of life *per se*, even if clearly related to the patient's liver disease, is not a sufficient indication for transplantation.

While the survival benefit of liver transplantation increases with increasing severity of liver disease (i.e. the MELD score), transplant recipients with very high MELD scores (30-40) utilize significantly higher health care resources to achieve similar outcomes than less sick patients. Thus, ideally liver transplantation would be performed in patients with a MELD score above 15 who are still in a reasonably good general condition (e.g. muscle mass, mobility).

Catastrophic complications and the need for life support may impair post-transplant outcomes to such an extent that liver transplantation has to be regarded as futile and should no longer be performed. Note that there are no uniformly accepted objective criteria to indicate this is the case; the decision to take a potential liver transplant recipient temporarily or permanently off the waiting list for "being too sick" therefore requires a team decision after thorough multidisciplinary assessment.

5. Deceased Donor Liver Allocation and Model for End-Stage Liver Disease (MELD)

The primary criterion for organ allocation in liver transplantation is urgency. In most programs, ABO blood group identity (or at least compatibility) between the donor and recipient is a prerequisite, because of otherwise inferior outcomes. Urgency means that the potential recipient with the highest mortality on the waiting list should first receive a liver for transplantation. In many programs/jurisdictions in Canada, livers are currently still allocated to potential liver recipients based on medical status (and within a given status, waiting time). Medical status is defined as follows: status 1, patient at home waiting for liver transplantation; status 2, patient hospitalized; status 3, patient in a step-down unit with renal failure and/or encephalopathy; status 4, patient in the intensive care unit (ICU), intubated and ventilated. Patients with fulminant liver failure receive a status 3F or 4F, and have a higher priority than other status 3 and 4 patients, respectively. Patients with an HCC are listed as a status 1T, and have a higher priority than other status 1 patients. This system is similar to the UNOS "status system" that was used in the United States up until 2002. However, the "status system," i.e. the location of a listed patient, does not necessarily correlate with medical urgency, i.e. with the patient's mortality on the waiting list. Thus, about 2/3 of all patients are listed as status 1, (i.e. at home), but their disease severity, (i.e. their mortality on the waiting list varies widely). In addition, waiting time used to break status ties, does not correlate with medical urgency. To overcome this shortcoming and to base liver allocation on objective parameters that better reflect waiting list mortality, the Model for End-stage Liver Disease (MELD) was developed.

The MELD score incorporates the patient's INR, bilirubin and serum creatinine. Scores are rounded to the nearest integer, and yield values from 6 to 40. MELD was originally developed as a predictor of survival in patients with end-stage liver disease undergoing insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS). MELD is the most accurate predictor of short-term (3 months) survival in patients with end-stage liver disease. Its predictive accuracy exceeds that of the older Child-Pugh score. The main features that distinguish MELD from the Child-Turcotte-Pugh (CTP) score (another system originally devised to predict survival in cirrhotic patients undergoing surgical shunts and subsequently used to predict survival in patients with advanced liver disease), is the absence of the two subjective clinical parameters, ascites and encephalopathy, and the incorporation and acknowledgement of renal dysfunction as a powerful predictor of survival in these patients.

MELD is based on three biochemical variables that are readily available, reproducible and objective. Table 3 demonstrates the MELD formula, and shows three-month mortality figures for potential transplant recipients based on MELD and Child-Turcotte-Pugh scores. MELD has repeatedly and independently been validated in large patient populations. Thus, the MELD score is the most accurate and best validated predictor of transplant urgency in potential liver transplant recipients available today.

In the USA, the MELD score has been used for liver allocation since 2002. More recently, some Canadian centers/jurisdictions have incorporated MELD, at least in some form, in their liver allocation algorithm.

6. Live Donor Liver Transplantation

Adult live donor liver transplantation (LDLT) evolved in the late 1990s to address the issue of relatively fixed liver supply (i.e. static organ donation rates), and the ever-increasing demand with growing liver transplant waiting lists and waiting list mortality. At the Toronto General Hospital, around 200 patients are currently wait-listed for a liver transplant, and waiting times for medical status 1 patients may easily reach several years. This waiting time leads to a waiting list mortality of around 20%.

In adults, LDLT consists of a right hepatectomy in a healthy person who has volunteered to donate part of their liver, and the subsequent transplantation of the donated right liver lobe into the recipient. The procedure can be safely performed only if certain anatomical and size requirements are met. To assure this, the liver donor undergoes an in-depth evaluation. This includes a thorough psychological evaluation to assure that the decision to donate is uncoerced, and that benevolence is its sole motivation.

The remnant left liver lobe in the donor and the transplanted right liver lobe in the recipient both regenerate within a couple of months, to a close-to-normal liver volume providing a normal liver function. LDLT is planed surgery, and allows for shortening of recipient waiting times. This is of particular benefit in situations where waiting time is critical for prognosis, i.e. the risk of drop out from the waiting list due to progression of disease, such as in HCC.

There are risks to the live donor, including a risk of death of up to 0.5%, as well as substantial morbidity. A highly publicized death of a donor in January 2002 subsequently tempered enthusiasm for live liver donation, and led to a decrease in LDLT activity in the USA. Presently, LDLT comprises less than 5% of total adult liver transplant activity in that country. The ethics, as well as the appropriate application of LDLT, continue to evolve in the USA and Canada. At the Toronto General Hospital, over 300 adult living donor liver transplants have been performed since April 2000, with no donor death and with both recipient and graft survivals

being similar to deceased donor liver transplantation. Given the lengthy waiting times and substantial waiting list mortality, most recipients are being offered LDLT in situations where a suitable living donor comes forward. Presently, only recipients who are candidates for deceased donor liver transplantation are being considered for LDLT. However, this practice may change as the ethics in this field evolve.

It is highly debated whether recipients with indications and/or a perioperative risks (co-morbidities) that would not normally be accepted for deceased donor liver transplantation should be accepted for LDLT when a suitable donor volunteers. This applies in particular to recipients with HCC and other tumors that fall outside current practice guidelines for liver transplantation, but also includes healthy elderly potential recipients. It is the policy in most liver transplantation programs that it is not justified to put a healthy donor at risk of morbidity and mortality when the recipient outcome is likely below the usually accepted futility threshold of a 50% 5-year survival.

7. Donation after Cardiac Death

The use of organs from donors who have died from a cardiac death, (i.e. had an irreversible cessation of circulatory function due to cardiac arrest), was the norm in the beginning of solid organ transplantation until the brain-death criteria were accepted some 40 years ago. In recent years, organ donation after cardiac death has been rediscovered, and is increasingly used in an attempt to address organ shortages. Donation after cardiac death occurs after the decision has been made to withdraw life support for medical reasons, in a hopelessly sick patient who does not fulfill brain-death criteria.

Donation after cardiac death can proceed in either a so-called controlled or uncontrolled fashion. In the controlled situation, life support is withdrawn in the operating room (OR) or intensive care unit (ICU), and organs are obtained after the patient has been pronounced dead, i.e. after a documented cardiac arrest of at least 5 min duration. In the uncontrolled situation, resuscitation measures in an urgent event are deemed futile and stopped. Many programs will accept donation after a controlled cardiac death, but, for ethical and logistic reasons, not in the uncontrolled situation. Donation after cardiac death invariably implies an agonal period of warm hypoxia/ischemia before the organs can be cooled by perfusion with preservation solution. While the hepatic parenchyma tolerates hypoxia/ischemia relatively well, the biliary tree is exclusively arterially perfused and is exquisitely sensitive to hypoxia/ischemia. Liver grafts obtained after cardiac death are therefore prone to develop ischemic type biliary strictures, with their associated morbidity and mortality. Nevertheless, transplantation of livers obtained after cardiac death can be life-saving, and several centers are currently working on improving its outcome.

8. Operative Procedure

Technical details of the procedure are beyond the scope of this discussion. However, the following salient points are worth mentioning: during the procedure the liver is mobilized and both the inflow to the liver and the inferior vena caval return to the heart are interrupted. This may cause hemodynamic instability, which can usually be managed without the use of a veno-veno bypass (in which the inferior vena cava [IVC] and portal blood are diverted through an extracorporeal bypass circuit to the axillary vein, and which was regularly used in the beginning of liver transplantation). The patient's original liver is subsequently removed, and the new liver graft is sewn in place. This involves anastomosing the IVC, the hepatic artery, the portal vein, and a duct-to-duct or biliary-enteric Roux-en-Y bile duct reconstruction. Although the liver is

flushed of the high potassium preservation solution prior to reperfusion, significant cardiac abnormalities can occur upon removing the clamps and reperfusing the liver. These intraoperative events demand a thorough preoperative assessment of cardiac status.

9. Postoperative Management

Issues that must be addressed in the postoperative period include: management of fluid, electrolytes and renal function; respiratory function; monitoring of neurologic status; immunosuppression; and graft function. While most patients are extubated within 24 hours of surgery, some can be extubated immediately after surgery and go directly to an intermediate care unit. In some recipients, ventilatory support may be needed for an extended period, particularly when the recipient is severely deconditioned, there is delayed graft function, presence of large pleural effusions, pulmonary infiltrates and/or diaphragmatic dysfunction or paralysis. Patients who were deeply encephalopathic prior to transplantation, in particular those with fulminant hepatic failure, may require an extended period of ventilatory support and ICU care.

Bleeding and bile leaks can occur early after surgery, and may require surgical re-intervention. Close clinical monitoring of the abdomen, of hemodynamics, and of blood hemoglobin concentration are mandatory in the early postoperative period.

Most patients are in a state of fluid overload after transplantation. These patients usually have a low serum albumin concentration, and respond well to colloid supplementation and diuretics. Renal insufficiency, occasionally requiring dialysis, is not uncommon postoperatively, particularly as patients deteriorate with lengthening waiting lists before they can undergo surgery. Renal failure may be due to a combination of factors, including preexisting intrinsic renal disease, hepatorenal syndrome, intraoperative blood loss and hypotension leading to tubular necrosis, drug induced nephrotoxicity (especially cyclosporine or tacrolimus), poor liver function, and sepsis.

Graft function resumes in the vast majority of cases immediately following transplantation. Abnormalities of coagulation are sensitive markers of hepatic dysfunction, and in most patients coagulation parameters should return to close to normal levels within 48 hours. Delayed graft function and primary non-function are rare events, and may present with coagulopathy, hepatic encephalopathy, hypoglycaemia, hyperkalemia or renal failure. The failure of coagulation parameters to normalize, especially if accompanied by encephalopathy and a hepatorenal pattern of renal dysfunction, is therefore an ominous sign of graft failure, and suggests the unfortunate need for retransplantation.

The causes of significant hepatic dysfunction within the first 48 hours include hepatic artery thrombosis, primary nonfunction, and very rarely accelerated cellular rejection. These can be difficult to differentiate on clinical grounds, and radiological investigations such as abdominal ultrasound with Doppler or angiography are required for diagnosis. Immediately following transplantation, narcotics and sedatives are kept to a minimum. Confusion and seizures may occur, and are usually related to metabolic disturbances (e.g., low serum magnesium levels), but are a recognized complication of both cyclosporine and tacrolimus.

10. Immunosuppression

There are many immunosuppressive agents available to the transplant physician. It is no longer a question of how to achieve adequate immunosuppression in order to avoid rejection. Rather, the issue is how to tailor immunosuppression with the different agents available (and their differing side effect profiles) to the specific needs of the individual patient. In liver

transplantation where acute rejection can almost always be managed with intravenous (IV) glucocorticoids ("steroids"), avoiding overimmunosuppression is clearly more important for good long-term outcome than avoiding rejection at any cost. While there is a wealth of data on the efficacy and safety of individual agents, the best combination of agents for certain populations, such as HCV-infected or insulin-resistant/diabetic recipients, remains to be defined.

- o *Corticosteroids.* In the vast majority of programs, all patients receive methylprednisolone perioperatively, typically starting at doses of 200-1000 mg preoperatively or in the operating room (anhepatic phase). Subsequently, i.v methylprednisolone is tapered, typically within 1-2 weeks, to an oral prednisone dose of 20 mg/day. In most programs, oral steroids are subsequently tapered and discontinued within three to six months. Major side effects include impaired wound healing, psychosis with the high perioperative doses, an increased incidence of infections (bacterial and fungal), insulin resistance/diabetes mellitus, weight gain, dyslipidemia, and osteoporosis. Steroid-free protocols typically replace steroids with induction using an IL-2 receptor antagonist (please see below) are feasible and safe. However, particularly in HCV patients, it remains to be shown if the steroid-free protocols improve outcome and are beneficial.

- o *Cyclosporine A.* The introduction of cyclosporine A (currently available in the microemulsified form as Neoral®) is one of the most important factors in improving results of liver transplantation. With its introduction, the one year graft survival increased abruptly from 30% to > 70%. Cyclosporine A binds to a specific cell protein, cyclophillin, and through a series of intracellular events prevents activation of T-cells and production of interleukin-2 (IL-2). The drug is given preferentially by the oral route; intravenous infusion is rarely required. In the early postoperative period, the dosage of cyclosporine A is adjusted to maintain a trough cyclosporine A level of 200-250 ng/mL, or a two-hour post ingestion level (C2) of 800-1,200 ng/mL. Daily monitoring of cyclosporine A levels in the immediate postoperative period is mandatory, as the drug has a narrow therapeutic index (efficacy vs. toxicity).

Cyclosporine A is metabolized in the liver by the P450 system (CYP3A4). Drugs that are metabolized or interfere with this hepatic drug metabolizing enzyme system will therefore affect cyclosporine A levels. For example, rifampicine and anticonvulsants such as carbamazepine induce CYP3A4 and thereby decrease cyclosporin A blood levels. Inhibitors of the P450 system, such as macrolide antibiotics (e.g. clarithromycine) and antifungals such as fluconazole, inhibit cyclosporine A metabolism, and lead to increased blood levels. These and many other drug interactions have to be kept in mind when starting transplant recipients on cyclosporine A on additional drugs.

Common side effects of cyclosporine A include renal dysfunction, tremor, headaches, arterial hypertension, dyslipidemia, weight gain and insulin resistance/diabetes mellitus. Hirsutism and gingival hyperplasia are less frequent.

- o *Tacrolimus (FK506; Prograf®).* Tacrolimus is a newer calcineurin inhibitor, and binds to FK binding protein before subsequently inhibiting T-cell activation by blocking IL-2 production, in a similar fashion to cyclosporine A. Monitoring is through trough levels, with a target of approximately 8-10 ng/mL early following transplantation. In the doses

clinically used, tacrolimus seems to be at least equally, and maybe slightly more immunosuppressive than cyclopsorine A. While most of the adverse effects of qualitatively similar with the use of immunosuppressants, insulin resistance/diabetes mellitus is more frequent with tacrolimus, and hirsutism as well as gingival hyperplasia is more frequent with cyclosporine A. Tacrolimus may play a role in the management of chronic rejection. Tacrolimus is metabolized in the liver similarly to cyclosporin A, and similar considerations regarding drug interactions apply.

o *Azathioprine (Imuran®)*. Azathioprine is a purine synthesis inhibitor, and as such inhibits the proliferation of cells, especially those rapidly dividing cells such as leucocytes (including T and B cells). Azathioprine is an old immunosuppressive agent that was routinely used in the early days of liver transplantation. Its side effects include bone marrow suppression. It has largely been replaced by the more potent mycophenolate preparations (please see below), and is only rarely used in transplantation today.

o *Mycophenolate Mofetil (MMF / Cellcept®)*. Mycophenolate, the active compound in MMF, is a potent reversible non-competitive inhibitor of inosine monophosphate dehydrogenase. It acts as a selective inhibitor of T- and B-cell proliferation by blocking the production of guanosine nucleotides and interfering with the glycosylation of adhesion molecules. The main side effect of MMF is bone marrow suppression. Importantly, it has no nephrotoxicity, and is an important agent in triple drug regimens, allowing a decrease in the dosage and therefore the toxicity of calcineurin inhibitors. Many patients experience significant gastrointestinal side effects from MMF, and dose modification is commonly required. Drug levels of MMF are not currently monitored in most transplant centres.

o *Mycophenolate sodium (MPA / Myfortic®)*. MPA is slow delayed release enteric coated galenic form of mycophenolate. Its immunosuppressive mechanisms of action, and its efficacy and side effect profile are identical to MMF. Whether gastrointestinal tolerability is improved due to the enteric coating remains debated.

o *Anti-Lymphocyte Products*. Anti-lymphocyte products can be monoclonal (OKT3) or polyclonal (ALG, ATG, thymoglobulin). In either case, the aim of therapy is to prevent or to treat rejection through lymphocyte, especially T-cell depletion. The use of these products has been associated with higher rates of viral infections, in particular cytomegalovirus (CMV), as well as an increased risk of (typically EBV-associated) lymphoproliferative disorders. OKT3 has been associated with side effects secondary to the release of cytokines (such as tumor necrosis factor and IL-1) that can range from mild flu-like symptoms, to life-threatening pulmonary edema and circulatory collapse. With other T-cell depleting agents having become available, OKT3 is therefore no longer used in most centers. In liver transplantation the use of these drugs is generally limited to induction immunosuppression in the presence of renal failure or significant neurologic dysfunction (to spare the use of calcineurin inhibitors), and in the treatment of the very rare steroid-resistant rejection.

o *Rapamycin (Rapamune®).* This secondary macrolide metabolite has a distinctly different mechanism of action than the calcineurin inhibitors. It binds to the FK binding protein, and inhibits the growth factor-dependent proliferation of hematopoetic and non-hematopoetic cells at the G1 to S phase, through the calcium-independent signals, called the mTOR pathway. Rapamycin effectively prevents allograft rejection (as well as reversing ongoing rejection), and is widely used in human renal transplantation. Rapamycin has antiproliferative effects *in vitro* and has therefore been proposed to be useful in liver transplantation for HCC, potentially reducing tumor recurrence rates. Clinical trials in this regard are ongoing. Rapamycin is not currently licensed for liver transplantation. In fact in the initial clinical trials, there was an increased hepatic artery thrombosis rate observed early post liver transplant. Side effects include bone marrow depression (anemia), impaired wound healing, and rarely there may be interstitial pneumonitis or proteinuria/nephrotic syndrome.

o *RAD (Everolimus®).* Similar to rapamycin, this compound is currently undergoing clinical trials in human liver transplantation. Recent studies have established its benefit in heart transplantation, where it has been shown to reduce chronic allograft vasculopathy.

o *IL-2 Receptor antagonists.* Basiliximab (Simulect®) and Daclizumab (Zenapax®) are IL-2 receptor specific monoclonal antibodies which inhibit proliferation of T-cells by binding to the alpha chain of the IL-2 receptor complex on activated T-cells. The IL-2 receptor antagonists have been shown to reduce the incidence of acute allograft rejection in kidney transplantation patients, and improve the one-year graft and patient survival. While the role of these agents in liver transplantation remains less well defined, they are used particularly in calcineurin- or steroid-sparing protocols.

o *Campath-1H.* Campath-1H is a humanized monoclonal antibody directed at CD52, a protein which is on lymphocytes and other cells of the immune system. It has been tested extensively in lymphoid malignancies, autoimmune diseases including rheumatoid arthritis, and multiple sclerosis. Its role in solid organ transplantation, in particular in liver transplantation, is not well defined. Immune cell depletion using Campath-1H allows the use of lower doses of maintenance immunosuppressive drugs, such as calcineurin inhibitors. This feature may be important in tolerance induction.

o *Other immunosuppressive agents.* There are several other immunsuppressive agents currently in early clinical development. These include belatacept, a chimeric antibody designed to inhibit the co-stimulatory signal during T cell activation, and sotrastaurin (AEB071), a protein kinase C inhibitor that prevents T lymphocyte activation.

11. Postoperative Complications
o Primary Non-function complications common to any surgical procedure can occur with liver transplantation. Several complications are peculiar to liver transplantation. The most concerning post-operative complication is *primary non-function (PNF)* of the new graft. Incidence rates of PNF range from less than 1% to over 5%. PNF becomes evident by persisting post-transplant symptoms and signs of liver failure, i.e.

coagulation parameters that worsen and cannot be corrected, increasing acidosis, deterioration in the patient's mental status (hepatic encephalopathy), and hepatorenal type renal failure. The etiology of PNF is unclear, and the treatment is urgent retransplantation.

o *Primary graft dysfunction* is a postoperative liver dysfunction of a lesser degree that may recover with time. The value of medical measures such as prostaglandin E-1 and/or N-acetyl cysteine in this situation is controversial, and none has been unequivocally proven to change outcome.

o *Vascular thromboses* that occur in the early postoperative period are generally technical in nature. Although thrombectomy of both portal vein and hepatic artery has been reported with some success, urgent retransplantation is usually required should these vessels thrombose early postoperatively.

o The *bile duct* has been termed the Achilles heel of liver transplantation. Bile duct problems occur in 10-20% liver transplantation cases. Early biliary leaks are secondary to ischemia, sepsis, or rarely to severe rejection. The bile duct can be irreversibly damaged in hepatic artery thrombosis immediately post transplant (ischemic type biliary injury).

o *Acute allograft rejection* (also termed acute cellular rejection [ACR]) occurs in about 20% of liver transplant recipients, usually in the first three months after transplantation. ACR is suspected in patients with rising liver enzymes. The pattern of enzyme elevation is non-specific and can be either hepatocellular (high serum concentrations of AST and ALT) or cholestatic (high bilirubin and alkaline phosphatase). Low grade fever, malaise and right upper quadrant discomfort can be present, but these are late findings and should not be required for the diagnosis of ACR.

o ACR is diagnosed by liver biopsy. Histologic findings of ACR include a mixed cellular periportal inflammation with mononuclear cells and eosinophils, bile duct injury, and endothelialitis, i.e. (sub)endothelial inflammatory changes in small portal and/or central veins. ACR usually responds to high dose steroid therapy (500 mg methylprednisolone i.v. daily for 3 consecutive days), followed by a gradual oral prednisone taper.

o The rare patient whose rejection fails to respond to IV steroid bolus therapy is usually rescued with a seven to 14 day course of an antithymocyte globulin preparation. Another approach is an intensification of the maintenance immunosuppression by switching to or increasing the dose of tacrolimus and/or adding a mycophenolate preparation.

o Late ACR episodes, i.e rejection episodes occurring after 3 months post transplant, are most frequently due to under-immunosuppression, be it secondary to malcompliance, therapeutic misadventures (drug interactions), or drug malabsorption (nausea/vomiting, diarrhea).

o Chronic Ductopenic Rejection: Failure of ACR to respond to immunosuppressive therapy, as well as other ill defined mechanisms, may result in *chronic ductopenic rejection* (CDR). CDR leads to the disappearance of small interlobular bile ducts, and eventually to biliary cirrhosis. CDR results in graft loss, i.e. the need for re-transplantation or death, in 2-5% of all liver transplanted recipients.

o *Infectious complications* are the major cause of death early following liver transplantation. The three main determinants of the risk of infection in transplant recipients are: those related to surgical problems e.g. bile leaks, the net state of immunosuppression and environmental exposure. Immunosuppressed patients are at risk for bacterial, viral and fungal infections. Bacterial infections with non-opportunistic organisms are usually seen in the early postoperative period, while opportunistic bacterial infections are seen one to two months or more after transplantation. Viral infections are seen frequently in immunosuppressed patients and usually occur at six weeks or later. The most important pathogen affecting transplant recipients is Cytomegalovirus (CMV). CMV causes both direct effects including tissue injury and clinical disease as well as a variety of indirect effects. In the absence of CMV prophylaxis, seronegative recipients of organs from seropositive donors have a greater than 50% risk of developing symptomatic disease. The diagnosis of CMV disease is accomplished by demonstrating viremia or tissue invasion. Patients who are mismatched, or those who receive anti-lymphocyte products, are therefore generally treated pre-emptively with ganciclovir or valganciclovir, often for three months following engraftment.

Other viral infections seen in the transplanted recipient include herpes simplex, Epstein-Barr virus, varicella zoster and adenovirus. Fungal infections are diagnosed in up to 20% of liver transplant patients and carry a significant mortality rate. Infections in general are usually proportionate to the degree of immunosuppression.

o *Malignant tumors* of all kinds, in particular EBV-associated post-transplant lymphoproliferative disorder (PTLD) and non-melanoma skin cancers, are well known consequences of immunosupression, and their risk of development is proportionate to the level and duration of immunosuppression. Malignant tumors are a major cause of mortality late after liver transplantation.

o *Cardiovascular events:* Steroids and calcineurin inhibitors increase the prevalence of cardiovascular risk factors such as obesity, insulin resistance/diabetes mellitus, arterial hypertension and dyslipidemia. One or a combination of these cardiovascular risks are present in a majority of liver transplant recipients who survive for more than one year post transplant. Not too surprisingly, therefore, the incidence of non-fatal and fatal *cardiovascular events* is increased around 3-fold in liver transplant recipients, as compared to a comparable normal population. In fact, cardiovascular conditions and malignancy are the most frequent causes of death occuring late after liver transplantation.

12. Results of Liver Transplantation

A one-year survival of >85% after liver transplantation is now typical. Most mortality occurs within the first 90 days, and is often related to the degree of pre-operative deconditioning and malnutrition of the recipient. After one year, few patients or grafts are lost and the 5 year survival rate for many indications exceeds 80% (see Table 4). Furthermore, a majority of patient rates their quality of life as normal or close to normal ≥6 months after surgery, and 60% of patients return to gainful employment. This demonstrates that liver transplantation is not only of benefit to the individual patient, but to society as a whole.

Although there are few reports of cost effectiveness, investigators from Pittsburgh and elsewhere have demonstrated that liver transplantation is less expensive than the costs of caring for similar patients treated for complications of cirrhosis. Indeed, the cost of a life year gained from liver transplantation is well below the US$ 50,000 generally accepted as the cost-effectiveness threshold. Patients with diseases that do not or only rarely recur after liver transplantation such as cholestatic liver diseases, have an excellent long-term prognosis (see Table 4).

In contrast, patients transplanted for hepatitis C have a poorer long-term outlook due to the almost universal recurrence of HCV infection in their graft. At least 10-30% of these patients progress within five years to cirrhosis, with its associated morbidity and mortality. Donor age, pre-transplant HCV RNA titers, and high dose steroid therapy for acute cellular rejection are among the most important determinants of the course of post transplant HCV recurrence and of patient survival. Having said that, recent data from Toronto and other centers show that overall up to 50% of these patients (40% genotype 1, 70-80% genotype 2/3) can be successfully treated with a pegylated interferon/ribavirin combination; HCV clearance halts disease progression and normalizes survival. Retransplantation of patients losing their graft due to HCV recurrence within 2-5 years is associated with poor patient and graft survival, and is not offered in most centers.

Table 4. Results of liver transplantation

Result	Cause of liver failure	Comments
➢ Excellent	o Cholestatic liver disease o Autoimmune hepatitis o Alcoholic cirrhosis (with appropriate patient selection) o Metabolic disease o Congenital disease o HBV (with HBIg and antiviral prophylaxis)	- Low recurrence rates
➢ Good	o HCV o HCC (small tumors)	- Moderate recurrence rates
➢ Fair	o Fulminant hepatic failure Retransplantation o Biliary atresia	- Results depend strongly on pretransplant status of patient
➢ Poor	o Large tumors o Cholangiocarcinoma	- High recurrence rates

13. Recent Advances and Future Directions

The availability of new immunosuppressive agents targeting different sites in the immunologic cascade offers the potential to individualize therapy for transplant patients. For example, starting patients with renal dysfunction or insulin resistance/the metabolic syndrome on a CNI-free immunosuppressive regimen may preserve their Glomerular Filtration Rate (GFR) or prevent the development of diabetes, respectively. Similarly, use of sirolimus and avoidance of CNIs in patients transplanted for hepatocellular carcinoma may improve long-term outcomes. Isolated hepatocyte or stem cell transplantation may offer treatment of metabolic and maybe other liver diseases. The former has already been successful in the laboratory setting.

While clinical trials have so far demonstrated little efficacy of available artificial liver support systems, they may eventually become successful in bridging patients to transplantation, or even allow for spontaneous recovery through normal hepatic regeneration, thereby reducing the need for transplantation. The elusive goal of tolerance has been produced in animal models, and if tolerance were induced in humans, this would obviate the need for immunosuppression and its associated complications.

As a step further forward, transcription profiling has been reported to allow identification of liver transplant recipients who have spontaneously developed operational tolerance. Xenotransplantation has moved to the farther horizon, but the use of transgenic animals may eventually offer a solution to the shortage of donor organs and permit a wider application of liver transplantation to liver disease.

Chapter 31: The Biliary System
E. A. Shaffer and J. Romagnuolo

1. Cholelithiasis

Gallstones (cholelithiasis; calculous disease) are the most common cause of biliary tract disease in adults, afflicting 20-30 million persons in North America. Approximately one-fifth of men and one-third of women will eventually develop cholelithiasis. In Canada, calculous disease of the biliary tract is also a major health hazard, accounting for about 130,000 admissions to hospital and 80,000 cholecystectomies annually. Cholecystectomy is the second most common operation in Canada and the United States, where it is performed six to seven times as often as in the United Kingdom or France. Although the frequency of gallstone disease does vary between countries and regions, it is high in both Western Europe and North America (Table 1). Laparoscopic cholecystectomy has further increased the use of surgery. Such variance suggests overuse of our health-care system, particularly as few (20%) individuals with cholelithiasis ever become symptomatic.

1.1. Classification of Gallbladder and Bile Duct Stones

Two major types of gallstones exist (Table 2).

1. *Cholesterol stones* are hard, crystalline stones whose composition is more than 50% cholesterol, plus varying amounts of protein and calcium salts. They predominate (> 85%) in developed countries.

2. *Pigment stones* are characterized by and acquire their colour from the insoluble pigment, calcium bilirubinate.

Table 1. Frequency of gallstone disease in different countries

Very Common (30-70%)	Common (10-30%)	Intermediate (<10%)	Rare (<0%)
o American Indians	o United States (whites)	o United States (blacks)	o East Africa
o Sweden	o Canada (whites)	o Japan	o Canada (Inuit)
o Chile	o Russia	o Southeast Asia	o Indonesia
o Czechoslovakia	o United Kingdom	o Northern India	o West Africa
o United States (Hispanics)	o Australia	o Greece	o Southern Africa
	o Italy	o Portugal	
	o Germany		

Table 2. Classification of Gallstones

Characteristic	Cholesterol	Pigment	
		Black	Brown
o Composition		- Pigment polymer - Calcium salts (phosphates, carbonates)	- Calcium birubinate - Calcium soaps (palmitate, stearate)
o Consistency	- Crystalline	- Hard	- Soft, greasy
o Location	- Gallbladder (+/- common duct)	- Gallbladder - Bile Ducts	- Common Duct
o Radiodensity	- Lucent (85%)	- Opaque (50%)	- Lucent (100%)

1.2. Basis for Gallstone Formation
1.2.1. Cholesterol Stones
Cholesterol gallstones form in three stages (Figure 1).
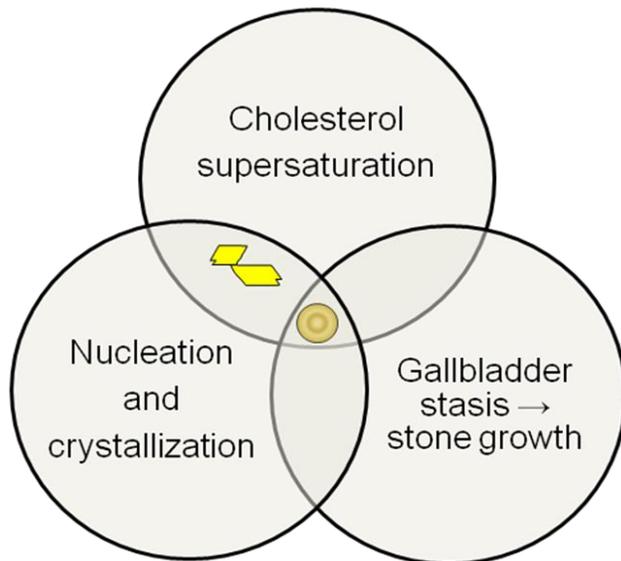
Figure 1. Three key stages in cholesterol gallstone formation, expressed as a Venn diagram: 1. Excess cholesterol secretion causes bile to become supersaturated; 2. Pronucleating proteins (especially mucins) then precipitate cholesterol microcrystals (shown as two notched rhomboids); and finally 3. Impaired gallbladder emptying in the final stage results in stasis that allows the time for these microcrystals to be entrapped in a mucin gel, which aggregates and attracts other insoluble components of bile (such as bile pigment and calcium), and so becomes biliary sludge and evolves into overt gallstones.

Cholesterol gallstones result primarily from an imbalance of the constituents of bile, aided by bile stasis. Bile is composed of three major organic molecules that are lipids: bile acids, phospholipids (phosphatidylcholine or lecithin) and cholesterol, in addition to its chief constituents: water and electrolytes. ATP-dependent transport proteins (ABC transporters), located on the canalicular membranes of the liver, actively secrete these lipids. In the first stage of cholesterol gallstone formation, the liver secretes excess cholesterol, forming supersaturated bile that cannot be solubilized by bile salts and lecithin. Certain genetic factors affecting the canalicular transporters are likely responsible, eliciting their phenotypic effect through exposure to environmental factors like female sex hormones and obesity. With time and in the presence of pronucleating agents particularly mucin gel, cholesterol microcrystals precipitate out of solution – the second stage. Mucin, a glycoprotein secreted by the gallbladder, then acts as a matrix scaffold for stone growth. The excessive cholesterol in bile also becomes incorporated into gallbladder smooth muscle, stiffens its sacroplasmic membranes, and so impairs signal transduction and contraction. In the third stage, gallbladder hypomotility and stasis facilitates retention, allowing the microcrystals to agglomerate and grow into overt gallstones.

"Biliary sludge" consists of calcium bilirubinate (formed from bilirubin), cholesterol microcrystals and mucin. On abdominal ultrasound, biliary sludge is echogenic material that layers but unlike gallstones, sludge does not cast an acoustic shadow. Sludge develops in association with conditions causing gallbladder stasis, such as during pregnancy or total parenteral nutrition. Though frequently asymptomatic and prone to disappear, sludge in the gallbladder can evolve into overt stones, or may escape into the biliary tract producing biliary-type pain, cholecystitis or even pancreatitis.

Risk factors for cholesterol gallstone formation are a family history (genetic), obesity/metabolic syndrome, female gender and aging. Certain ethnic groups such as First Nations persons are especially prone to cholelithiasis (Table 3).

Table 3. Mechanisms and clinical presentation for gallstone formation

	Cholesterol gallstones	Black pigment stones	Brown pigment stones
➢ Mechanisms	o Excessive cholesterol secretion	o Chronic hemolysis o Altered bilirubin metabolism o Excessive bilirubin excretion	o Stasis o Strictures
➢ Associations	Metabolic: o Family history o Obesity/Metabolic syndrome o First Nations person o Female sex hormones o Aging	o Cirrhosis o Cystic fibrosis o Crohn disease o Advanced age	o Infection o Inflammation

1.2.2. Pigment Stones

Black pigment stones constitute about 15% of gallstones found at surgery (cholecystectomy) in North America, These small, hard gallstones are composed of calcium bilirubinate as a polymer plus inorganic calcium salts (e.g., CaCO3, CaPO4). The basis for their formation is excessive (or abnormal) bilirubin excretion in bile. They tend to form in alcoholic patients, chronic hemolytic states and with old age. (Table 3) Curiously, pigment stones also are associated with bile salt malabsorption. When ileal disease or loss causes bile salts to escape into the colon (especially the cecum) in large quantities, this biological detergent can then solubilize the bile pigment and return it via the portal vein to the liver. This creates an enterohepatic circulation for pigment material whose subsequent secretion into bile becomes excessive, creating black pigment stones.

Brown pigment stones, soft and greasy, are composed of bilirubinate and fatty acids that respectively account for their color and slippery texture. These brown stones form in bile ducts associated with inflammation, infection (often from a stricture or tumor) or parasitic infestation (e.g., liver flukes) of the biliary tract. Bacteria and inflamed tissues release ß-glucuronidase, an enzyme that deconjugates bilirubin. The resultant free bilirubin then polymerizes and complexes with calcium to form calcium bilirubinate that precipitates in the bile duct system. Hydrolytic enzymes, acting on phospholipids, meanwhile produce fatty acids like calcium palmitate and stearate. Biofilm, a glycoprotein produced by bacteria as their glycocalyx, then agglomerates this pigment material, leading to brown stones. Stagnation and recurrent infection predispose to chronic cholangitis and eventually in some, cholangiocarcinoma.

1.3. Natural History of Gallstone Disease

Gallstones grow at the rate of about 1-2 mm per year, over a five- to 20-year period, before symptoms develop (often symptoms never develop). Gallstone disease is a common problem, affecting 10 to 15% of adults in developing countries, yet most (80%) never develop symptoms or complications. Gallstones frequently are clinically "silent," being incidentally detected on routine abdominal ultrasound performed for another purpose. If problems do occur, the symptoms usually arise in the form of biliary pain (at a frequency of about 2% per year during the first five years, and then decreasing over time). Thus, biliary pain rather than a biliary complication represents the initial manifestation in most (90%) people with previously asymptomatic gallstones. As the rate of a biliary complication is very low (3% at 10 years), prophylactic cholecystectomy is not warranted in those with stones who lack symptoms.

Complications arise when stones in the gallbladder:
1. Obstruct the cystic duct, leading to cholecystitis: this begins as a chemical inflammation that later may become complicated by bacterial invasion; or
2. Pass out of the gallbladder into the common duct and either obstruct the bile ducts (producing biliary pain and cholestasis), often accompanied by bacterial infection in the bile ducts (cholangitis), or lodge in the common pancreatobiliary channel, temporarily blocking the pancreatic duct (or causing bile reflux into the pancreatic duct) and resulting in pancreatitis (Figure 2).
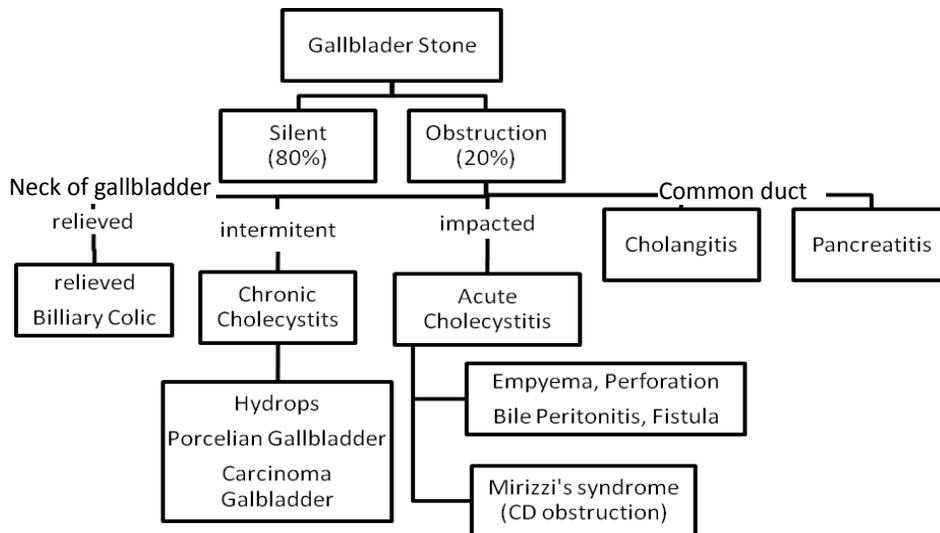
Figure 2. Potential complications of cholelithiasis.

Migration of the stone in the gallbladder to impact in the neck of the gallbladder or the bile duct can cause obstruction and result in complications. Cystic duct obstruction results in cholecystitis. It is often suggested that chronic calculous cholecystitis may be associated with carcinoma of the gallbladder, but causality is unproven. Common duct obstruction leads to cholangitis, cholestatic jaundice and/or pancreatitis. Chronic cholestasis results in malabsorption of lipids. Stricture formation and recurrent cholangitis on occasion can lead to secondary biliary cirrhosis. Chronic duct obstruction and injury may lead to cholangiocarcinoma.

1.4. Clinical Features

Biliary colic ensues when a stone obstructs the cystic duct, causing sudden distension of the gallbladder. "Colic" is a poor term, as biliary pain typically does not increase and decrease spasmodically. Rather, the right upper quadrant or epigastric pain begins rather suddenly, quickly becomes intense, remains steady for 15 minutes to some six hours and then gradually disappears over 30 to 90 minutes, resolving spontaneously (though occasionally there remains a transient, vague ache for up to a few days). Its duration is seldom shorter than 15 minutes and is often sufficiently severe for many sufferers to seek medical attention and to require narcotics for relief.

Although biliary-type pain can follow a large meal, the old adage "fatty food intolerance" is not specific for biliary tract disease. Such dyspepsia is more a feature of a functional gut problem. A more regular (even daily) pattern of crampy abdominal pain, particularly when relieved by defecation, accompanied by a history of bloating and altered bowel motions suggests the irritable bowel syndrome (IBS) rather than a clinically "innocent" gallstone.

Biliary colic is a visceral pain that is steady and deep-seated. The pain is poorly localized in the right upper quadrant (RUQ) or central epigastric area. Lower abdominal pain from biliary disease is rare. Movement does not aggravate it. Mediated by splanchnic nerves, biliary colic may radiate like angina to the back, right scapula or shoulder tip, down the arm or into the neck, or even rarely biliary colic pain may be confined to the back. The patient is usually restless, and

may exhibit vasomotor features such as sweating and pallor. Nausea with some vomiting may accompany a severe attack. Fever and rigors are absent when they cystic duct is obstructed and there is no inflammation. Such presence of fever and rigors suggest that a stone has migrated and become lodged in the cystic duct, causing cholangitis, or that the gallbladder is acutely inflamed (acute cholelithiasis).

Findings consist of mild-to-moderate right upper quadrant or epigastric tenderness. There are no peritoneal signs. Indeed, the examination is often quite normal, especially between attacks. Laboratory tests are characteristically normal.

Once gallstones are complicated by an attack of biliary pain, a recurrent pattern is likely to ensue, days or weeks apart. Symptomatic gallstones have a more aggressive course than those that are asymptomatic. Episodes of even uncomplicated biliary pain tend to recur at nearly 50% per year. Although 30% of patients with one episode of biliary pain do not have further episodes, most experience a recurrent pattern that remains fairly constant. These episodes may be sporadic separated by pain-free periods lasting from days to years, during which the patient feels well and the liver biochemistry is normal. However, complications requiring surgery may arise at any time, with a frequency of 1 to 2% per year. Pain lasting more than six to 12 hours, especially if accompanied by persistent vomiting or fever, suggests another process such as cholecystitis or pancreatitis (Table 4).

Table 4. Comparison of biliary colic to acute cholecystitis

	Biliary colic	Acute cholecystitis
o Pain	- Constant - visceral	- Constant - parietal
o Duration	- < 6 hours	- Hours to days
o Nausea /Vomiting	- Some nausea	- More prominent - after pain onsets
o Onset	- Rapid	- Variable
o Jaundice	- No	- Later in 20%
o RUQ Tenderness	- Modest	- Marked, with guarding (Murphy's sign)
o Fever	- No	- Yes
o Leukocytosis	- Absent	- Present
o Resolution	- Spontaneous, in < 6 h	- Spontaneous in ~½, but 10% risk septic complication (abscess, perforation)

1.5. Diagnostic Imaging

Detecting gallstones (as opposed to diagnosing clinically symptomatic gallstone disease) is by diagnostic imaging. Plain abdominal x-rays will only identify the 10-15% with high calcium content as radiopaque densities in the right upper quadrant. Ultrasonography is the most sensitive and specific method for detecting gallstones (appearing as echogenic objects that cast an acoustic shadow) or a thickened gallbladder wall (indicating inflammation). (Figure 3) Small stones (<2-3mm) can be missed on abdominal ultrasound. MRCP (magnetic resonance cholangiopancreatography) is non-invasive test that can also detect gallstones, but is costly.

Abdominal CT scan is less sensitive than ultrasound to detect stones, unless the patient is obese. Also, if the gallbladder is fibrotic and shrunken, ultrasound may not visualize the gallbladder.

1.6. Management

Once symptoms develop (e.g., as biliary colic), repeated attacks are likely. Although most episodes of biliary colic resolve spontaneously, pain eventually recurs in 20-40% each year. Furthermore, complications such as cholecystitis, choledocholithiasis, cholangitis or gallstone pancreatitis emerge at a frequency of 1-2% per year, often necessitating emergency cholecystectomy. Because of recurrent attacks of pain and these increased risks, cholecystectomy is indicated once biliary colic develops. The risk of any emergency procedure is greater then elective surgery, so this is why elective cholecystectomy is recommended.

Figure 3. Abdominal ultrasound of two gallstones. In addition to each being echogenic, they each cast an acoustic shadow.

1.6.1 Medical Therapy

Uncomplicated biliary pain will respond to general medical support, and the judicious use of analgesics such as meperidine and nonsteroidal anti-inflammatory drugs (NSAIDs) like diclofenac.

Bile Acid Dissolution of Cholesterol Gallstones

Administered orally, the bile acid, ursodeoxycholic acid (UDCA), lowers cholesterol saturation in bile and can dissolve gallstones. Such therapy has limited value because of a high recurrence rate of stones (50% at five years), and limited applicability: stones ideally should be small (<5 mm is best) and composed of cholesterol (radiolucent), while the gallbladder must fill/empty (by HIDA scanning, or by oral cholecystography now rarely used). UDCA is reserved to prevent gallstone formation in obese individuals undergoing rapid weight loss via dietary caloric restriction or bariatric surgery.

1.6.2. Cholecystectomy
1.6.2.1. Open cholecystectomy

The term "open" connotes the need for an incision to open the abdominal cavity for direct visualization in the course of removing the gallbladder. Open cholecystectomy is usually necessary in Mirizzi's syndrome, an infrequent complication in which large gallstones compress

and so obstruct the common bile duct. Mortality of open cholecystectomy is low at <0.5%, but reaches 3% for emergency surgery in acute cholecystitis or for common duct procedures, and is high in the elderly with co-morbid conditions. The open technique has largely been replaced by laparoscopic cholecystectomy.

1.6.2.2. Laparoscopic cholecystectomy

This minimally invasive technique employs an endoscope that displays large images on a TV monitor to view the abdominal contents (with the peritoneal cavity insufflated with gas) and uses instruments (like clips, scissors and graspers) inserted through small incisions in the abdominal wall to perform surgical manipulation. In addition to the obvious cosmetic appeal, these smaller incisions result in less postoperative pain and shortened recovery time, allowing an early discharge from hospital (sometimes the same day as an outpatient) and return to work. The disadvantages include a somewhat higher complication rate, particularly from common duct injury and retained common duct stones, plus the potential for overuse. In 5% of cases the procedure must be converted to an open cholecystectomy because of technical problems. Laparoscopic cholecystectomy is now the standard for elective removal of the gallbladder in those with significant symptoms (e.g., necessitating repeated visits to the emergency room for narcotic relief) or with complications. Prophylactic cholecystectomy is not warranted in those with asymptomatic stones except for rare cases suspected of developing/ harboring carcinoma of the gallbladder (e.g., very large stones > 3 cm or a calcified gallbladder wall termed the "porcelain gallbladder").

1.6.2.3. Notes

Natural orifice transluminal endoscopic surgery (NOTES) is an experimental endoscopic technique that uses a natural orifice (such as the mouth, anus, or vagina) and then an endoscopically created internal incision (like through the stomach or colon) as the route through which instruments are passed via an endoscope to perform an operation and retrieve the specimen. Transgastric and transvaginal cholecystectomies have been successfully performed in humans, avoiding external abdominal incisions and scars, although to date these have mostly been done as a "hybrid" technique, involving a single laparoscopic port in addition to the NOTES instrument. Pure NOTES human experience for cholecystectomy is scant. It remains unclear if improvements in cosmetic and potential recovery time will be outweighed by the much longer operative time and other potential adverse events of NOTES cholecystectomy.

2. Cholecystitis
2.1. Chronic Calculous Cholecystitis

Chronic inflammation of the gallbladder is the most common histological process, often manifest as mild fibrosis of the gallbladder wall with a round cell infiltration and an intact mucosa. Some degree of chronic inflammation inevitably accompanies gallstones, but the stones will have developed first. Even transient obstruction of the cystic duct can produce biliary colic and an element of inflammation that is chemical in origin. There is little correlation between the severity and frequency of such biliary episodes and the degree of inflammation or fibrosis. Chronic inflammation thus may follow the resolution of acute cholecystitis, evolve with recurrent episodes of biliary colic or develop insidiously. It is the presence of true biliary colic which drives the indication for cholecystectomy, not the possible presence of chronic cholecystitis.

2.1.1. Clinical Features

The clinical features are those of either biliary colic or a previous episode of acute cholecystitis that has resolved leaving the gallbladder chronically inflamed and scarred. The pain characteristically is a constant dull ache in the right upper quadrant or epigastrium, and sometimes also in the right shoulder or back. Nausea is frequent. Flatulence, fatty food intolerance and dyspepsia occur, but are equally frequent in patients without gallstone disease. Fever or leukocytosis suggests acute cholecystitis or another entity. There may be local tenderness in the right upper quadrant of the abdomen but no peritoneal findings.

2.1.2. Diagnosis

Diagnosis largely depends upon detecting gallstones, either by plain films of the abdomen or CT (10-15% are calcified) or preferably by abdominal ultrasonography (95% accuracy). In addition, ultrasound (or CT) can identify signs of inflammation, such as free fluid around the gallbladder, and/or gallbladder wall thickening. If the gallbladder is fibrotic and shrunken, ultrasound visualization may be difficult. A nuclear medicine cholescintigraphy scan may be positive with the gallbladder failing to fill, but non-visualization is rather insensitive for chronic cholecystitis, because of frequent false positive and false negative tests.

2.1.3. Management

Once symptoms begin, they are most likely to recur, whereas asymptomatic stones, or stones associated with dyspepsia without biliary colic, are generally treated expectantly. Medical management depends upon gallstone size, gallbladder function and any co-morbid conditions (e.g., age, obesity, diabetes). Cholecystectomy provides definitive treatment, removing the stones and the gallbladder, and eliminating recurrences of true biliary pain.

2.2. Acute Cholecystitis

Here the gallbladder becomes acutely inflamed. In most (>90%), a stone has obstructed the cystic duct for a prolonged period, resulting in a vicious cycle of increased secretion of fluid, causing distension, mucosal damage and the release of chemical mediators of the inflammatory process. Inflammatory damage is primarily chemical. Bacterial infection is a late complication. Obstruction of the cystic duct results in the gallbladder becoming distended with bile plus an inflammatory exudate or even pus. The gallbladder wall can become thickened and go on to necrosis and perforation. If resolution occurs, the mucosal surface heals and the wall becomes scarred, but the gallbladder may not function – e.g., may not fill on HIDA or oral cholecystography.

In a minority, acute cholecystitis can occur in the absence of obvious stones (*acalculous cholecystitis*). Although acalculous cholecystitis can occur in healthy individuals, it tends to affect elderly men who have co-existent vascular disease, debilitated individuals and even young children. (see section *3.2.1* below)

2.2.1. Clinical Features

Acute cholecystitis begins like biliary colic (Table 4). The abdominal pain rises to a plateau and remains constant. Its location is usually the right upper quadrant or epigastrium, sometimes radiating to the back or the right shoulder. There may be a previous history of biliary pain (in ~75%). Pain in acute cholecystitis, unlike biliary colic, persists for more than six to 12 hours. As the gallbladder becomes inflamed, the visceral pain is replaced by parietal pain, which

is better localized and is aggravated by movement. Once the pain begins, nausea and vomiting often follow. Fever is usually low-grade in the absence of perforation or abscess formation. If rigors occur, one should suspect a bacterial infection and/or bacteremia. Abdominal examination characteristically shows tenderness in the right upper quadrant. During palpation of the right upper quadrant, a deep breath may worsen the pain and inspiration suddenly ceases (Murphy's sign). Severe cases exhibit peritoneal signs of guarding and local rebound tenderness. A reflex paralytic ileus may be present. Patients appear unwell and are reluctant to move with such parietal pain. An enlarged gallbladder is sometimes palpable, particularly with the first attack before fibrosis contracts it.

2.2.2. Diagnosis

Leukocytosis is common. Blood cultures may be positive. Liver biochemistry is often normal. Clinical Jaundice with mild hyperbilirubinemia (<2x normal) and elevated liver enzymes occur in about 20% of cases, even in the absence of common duct stones. Cholestasis can develop from either a concomitant bile duct stone, or a distended gallbladder that compresses the common duct (Mirizzi's Syndrome). Markedly elevated bilirubin levels suggest that a stone resides in the common duct. High levels of aminotransferase or alkaline phosphatase imply a common bile duct stone. A elevated amylase or lipase indicates gallstone pancreatitis from a bile duct stone that has recently been present; but most times (80%)the stone will have already passed on its own. A hepatitis-like picture (high aminotransferase) often develops from liver bed inflammation due to the cholecystitis, but could be an early indication that a stone has passed into the common duct even before the blood concentration of bilirubin, alkaline phosphotase or GGT rises.

The clinically suspected diagnosis of acute cholecystitis is best confirmed by ultrasound, which detects the stone(s) and a thickened gallbladder wall. In doing the procedure, the radiologist may elicit marked tenderness when pressing over the gallbladder (the ultrasonographic Murphy's sign). In suspected cases of acute cholecystitis, cholescintigraphy (HIDA), a nuclear medicine scan, assists the diagnosis by failing to fill the gallbladder with radionucleotide because of a stone obstructing the cystic duct. Non-visualization also can occur in chronic cholecystitis due to failure to concentrate and in cholestasis because of impaired marker secretion.

2.2.3. Management

The definitive treatment is cholecystectomy (surgical removal of the gallbladder). General measures include rehydration, observation, analgesia and antibiotics. In mild cases of acute cholecystitis that resolve, cholecystectomy can be delayed for up to six weeks. Because of the risk of recurrent cholecystitis, surgery (usually as a laparoscopic cholecystectomy) should generally be performed soon after the current admission, once the patient has been stabilized.

2.2.4. Complications

Acute cholecystitis usually resolves spontaneously, usually within 3-7 days. Inflammation may progress to necrosis, empyema or perforation in about 10% of cases if untreated. These complications will be heralded by: (1) a continuation of the pain, along with tachycardia, a high fever, peritoneal signs and marked leukocytosis; (2) features of a secondary infection, such as empyema or cholangitis; or (3) a suspected perforation. Emergency cholecystectomy then becomes mandatory.

Empyema is a suppurative cholecystitis with an intraluminal abscess (i.e., inflamed gallbladder containing pus). It develops from continued obstruction of the cystic duct leading to secondary infection. The abdominal findings of acute cholecystitis are accompanied by systemic features of bacteremia, with fever and rigors. Treatment includes analgesics, antibiotics, IV fluids and prompt cholecystectomy.

Perforation of the gallbladder occurs when unresolved inflammation leads to necrosis of the wall, often in the fundus (a part of the gallbladder that is relatively avascular). Gallstones also may erode through a gangrenous wall. Free perforation with bile peritonitis is fortunately uncommon, as the mortality reaches 30%. If localized, the perforation spawns an abscess, clinically evident as a palpable, tender mass in the right upper quadrant. The pain and temperature may also transiently resolve, only to be replaced by acute peritonitis. Both localized and free perforations demand surgery, with or without preoperative percutaneous drainage of the abscess. Rupture into adjacent viscera (e.g., the small intestine) is rare; this creates an internal biliary fistula. Large stones that pass through this type of fistula can produce a mechanical small intestine obstruction (*gallstone ileus*). Obstruction usually occurs at the terminal ileum, rarely at the duodenal bulb or the duodenojejunal junction. Radiologic diagnosis comes from finding air in the biliary system, a small bowel obstruction and perhaps a calcified gallstone ectopically located. Urgent surgery with appropriate antibiotic coverage is imperative.

Hydrops of the gallbladder occurs when the inflammation subsides but the cystic duct remains obstructed. The lumen becomes distended with clear mucoid fluid, the bile pigment having been reabsorbed. The hydropic gallbladder is evident as a right upper quadrant mass that is not tender. Treatment is cholecystectomy.

Limy bile occurs when prolonged gallbladder obstruction causes loss of the pigment material from bile and the residual calcium salts precipitate. The hydropic, obstructed gallbladder secretes calcium into the lumen. *Porcelain gallbladder* occurs when calcium accumulates in the wall of the gallbladder, readily identified on abdominal plain films. Although presumably there has been at least one episode of acute cholecystitis in the past, most patients with a porcelain gallbladder are asymptomatic. One-quarter will develop carcinoma of the gallbladder, prompting the need for prophylactic cholecystectomy.

2.3. Choledocholithiasis

Stones in the common bile duct (aka choledoccholithiasis) are classified according to their site of origin: *primary stones* form in the bile ducts; *secondary stones* originate in the gallbladder and then migrate into the common duct. In North America, virtually all cholesterol stones and most pigment stones are considered secondary when the gallbladder is intact. Thus, more than 85% of patients with common duct stones also have stones or sludge in the gallbladder. Conversely, about 10% of patients undergoing cholecystectomy for chronic cholecystitis also have common duct stones. *Residual stones* are those missed at the time of cholecystectomy; *recurrent stones* develop in the ductal system more than three years after surgery.

The composition of stones also varies with their site of origin. Stones are predominantly (approximately 80%) cholesterol when situated in the gallbladder and in the common duct. After cholecystectomy, the proportion of ductal stones that are pigment rises with time: most recurrent ones (more than three years after surgery) are pigment stones. These brown stones result from stasis (e.g., a postoperative stricture or a tumor) and infection.

2.3.1. Clinical Features

Most common duct stones eventually become symptomatic, causing biliary colic, obstructive jaundice, cholangitis or pancreatitis (Figure 2). Biliary colic results from sudden obstruction of the common duct, which increases biliary pressure. The abdominal pain is steady, located in the right upper quadrant or epigastrium, and can bore through to the back.

Acute cholangitis results when duct obstruction leads to infection. Obstruction and ductal damage permit bacteria to regurgitate across the ductal epithelium into the hepatic venous blood, causing a bacteremia with chills and a spiking fever, hence the concept of it being "pus under pressure". The raised intrabiliary pressure also causes abdominal pain. The classical "Charcot's triad" consists of jaundice, upper abdominal pain and fever. Jaundice results from the mechanical obstruction of the ducts plus a component of intrahepatic cholestasis due to sepsis (endotoxin, for example, impairs hepatic bile formation). Pain and fever are common, though jaundice may not be clinically apparent on presentation. There is abdominal tenderness; a large, tender liver should raise a suspicion of coexistent liver abscesses. Hypotension, confusion and a septic picture predominate in critical cases.

Pancreatitis can result from gallstones impacting at the ampulla of Vater. Acute pancreatitis consists of "pancreatic"-type pain (epigastric, often radiating to the back), elevated pancreatic enzymes (amylase/lipase >3 times the upper limit of normal) and radiologic evidence of pancreatic inflammation. The basis for gallstone pancreatitis is either from a stone obstructing the pancreatic duct at the ampulla, or from bile refluxing into the pancreas, if the stone is impacted in a common biliopancreatic channel. Acute biliary pancreatitis does not differ clinically from other forms of acute pancreatitis. Gallstone pancreatitis tends to be more commonly associated with jaundice and higher serum levels of bilirubin, alkaline phosphatase and aminotransferase than alcohol-induced pancreatitis, but there is considerable overlap. Ultrasound should detect any stones in the gallbladder in addition to the inflamed pancreas, with or without biliary dilatation, but gallbladder imaging in the acute setting may be limited due to tenderness (inability to perform certain maneuvers) and associated ileus (gas-filled stomach/intestine obscuring areas). In the absence of alcohol as a factor, pancreatitis in the setting of gallbladder stones/sludge is presumed "biliary" in etiology. Most non-alcoholic pancreatitis is due to gallstones, so repeating an ultrasound after an attack is settled may be needed to rule out occult cholelithiasis missed on the first normal (perhaps limited) study.

2.3.2. Diagnosis

Mild leukocytosis and abnormal liver biochemistry are common. Although usually cholestatic in pattern, the liver enzymes may be predominantly hepatitis-like (aminotransferases spiking to 1000IU/l or more, and being more prominent than alkaline phosphatase increase) in the early phases of the attack. Urine may be positive for bilirubin and then appears tea-colored (which some patients interpret incorrectly as hematuria).

Diagnostic imaging is the key to identify duct dilatation as the hallmark of obstruction and to clarify the cause. Ultrasound (the diagnostic imaging technique of choice) will often show dilated ducts >6 mm and, in advanced cases, liver abscesses. Ultrasound is highly specific for duct dilation (80% sensitivity), though insensitive for the biliary stone itself (30-40%). A previous cholecystectomy can result in bile ducts up to 10 mm in size without any obstruction; such dilation develops slowly after removal of the gallbladder rather than being an immediate event. Indeed, the common duct even dilates slightly with age at ~1 mm every decade above the age of 60.

Hepatobiliary scintigraphy is insensitive. Helical CT cholangiography can detect biliary dilatation and bile duct stones, but is primarily used to evaluate complications such as liver abscesses.

Magnetic resonance cholangiopancreatography (MRCP) uses a heavily T2-weighted technique to clearly depict the fluid-filled biliary and pancreatic ducts without the need for contrast agents. MRCP is non-invasive, highly sensitive and specific for detecting stones and ductal dilatation, and identifying the site of biliary obstruction (Figure 4A).
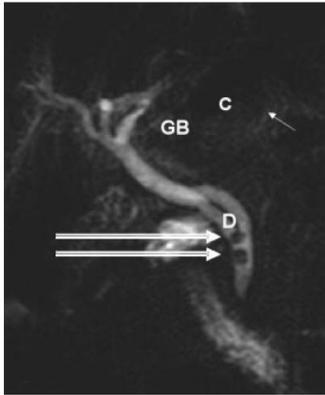
Abbreviation: D, Duodenum; GB, gallbladder; C, cystic duct.

Figure 4A. MRCP showing 2 stones (large arrows) in the common duct. Small arrow indicates the pancreatic duct.

Endoscopic ultrasound (EUS) uses a specialized endoscope with an ultrasound probe at the tip (echoendoscope) to image the bile duct through the apex of the duodenum, under conscious sedation. It is also highly sensitive and specific for ductal stones and is likely more sensitive than MRCP when biliary dilatation is absent and/or when stones are small (< 5 mm) (Figure 4B).

Although both MRCP and EUS are very accurate, they are generally indicated for patients with low/intermediate probability for a stone, they are not used in patients with cholangitis since a negative test will not change the decision to go on to ERCP.
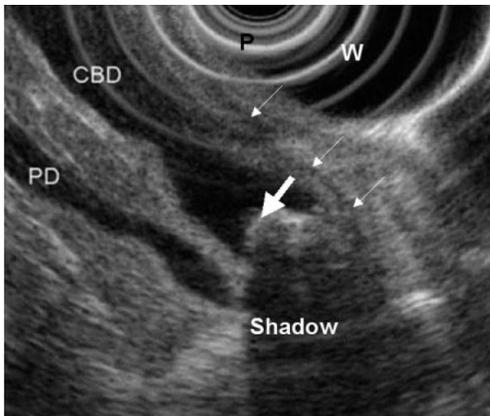
Figure 4B. A radial endoscopic ultrasound image showing part of a "stack sign" imaged through the duodenal bulb (common bile duct (CBD) pancreatic duct (PD) and portal vein (not shown) in long-axis view, seen as dark (hypoechoic) stripes parallel to one another). A wedge shaped dark (hypoechoic) acoustic shadow is seen behind the bright (hyperechoic) 4-5 mm stone (arrow), making even this small stone appear quite obvious. P=probe at tip of scope; W= water filled balloon around probe. Small arrows indicate tangential view of duodenal wall.

ERCP (endoscopic retrograde cholangiopancreatography) was the "gold standard" for biliary imaging. Because of the need for conscious sedation and the injection of dye into the ampulla of Vater, this invasive procedure is associated with a 2-5% risk of pancreatitis. Moreover, in the 1% complicated by severe pancreatitis, mortality reaches 10%. ERCP is thus no longer used as a primary diagnostic tool but does offer important therapy: cutting open the sphincter of Oddi with cautery (sphincterotomy) to remove stones, sometimes assisted by lithotripsy (stone fragmentation) and/or stenting. Bleeding, perforation, and cholangitis are other rare complications.

2.3.3. Management

General medical care should include blood cultures and broad spectrum antibiotics to cover gram-negative microorganisms, anaerobes, and enterococcus: e.g., gentamycin, metronidazole and ampicillin. Noninvasive biliary imaging (MRCP, EUS) is most appropriate for scenarios with a low to intermediate probability of ductal stones, as an ERCP will follow in only a few cases. Intermediate to high probability situations (e.g., cholangitis, jaundice, biliary dilatation) have a higher probability of requiring a therapeutic ERCP (sphincterotomy and stone removal), and generally should go directly to ERCP.

Acute cholangitis represents a medical emergency that necessitates urgent decompression of the biliary system. ERCP with sphincterotomy followed by extraction of the stone is definitive therapy for cholangitis. If ERCP is unavailable or unsuccessful, percutaneous transhepatic cholangiography (PTC) decompresses the biliary tract and provides drainage that should be maintained, awaiting permanent relief of obstruction. Surgical bile duct exploration is rarely needed. Laparoscopic cholecystectomy should then be done electively, preferably within a few weeks of the attack. Although open cholecystectomy with common duct exploration will remove the gallbladder and all biliary stones, this once standard procedure carries with it a longer recovery period and a higher operative morbidity than the combination of ERCP with laparoscopic cholecystectomy. Laparoscopic exploration of the common bile duct is technically difficult and generally restricted to stones < 7-8 mm.

In *gallstone pancreatitis*, bile duct stones will pass spontaneously into the duodenum in about 70% of patients. Rising liver enzymes over subsequent days, bilirubin more than twice normal and ultrasonographic evidence for biliary dilatation represent independent predictors of a retained stone. In mild-to-moderate gallstone pancreatitis, MRCP or EUS should be performed. ERCP is reserved for patients with increasing liver enzymes, jaundice or biliary dilatation. In severe pancreatitis, cholangitis, or ongoing biliary obstruction (as evidenced by jaundice, ultrasonographic biliary dilatation), early ERCP (within 24-48 hrs) and sphincterotomy becomes warranted.

Once ERCP clears bile duct stones, cholecystectomy should follow, ideally prior to discharge, but preferably in the following few weeks as recurrent biliopancreatic problems are frequent in the next few months. Unlike alcoholic pancreatitis, gallstone-related disease does not progress to chronic pancreatitis, unless the acute attack was associated with necrosis and permanent damage, such as a pancreatic stricture.

3. Acalculous Gallbladder Disease And Postcholecystectomy Syndromes

3.1. Congenital Anomalies

Congenital abnormalities of the gallbladder and biliary system result from embryonic maldevelopment. They are pertinent for the surgeon attempting to identify biliary anatomy at cholecystectomy. Agenesis of the gallbladder is rare. Curiously, it is associated with common duct stones, likely because the duct attempts to take over some of the reservoir role of the gallbladder. This topic is covered in specialized texts.

3.2 Painful Acalculous Gallbladder Disorders

3.2.1. Acute Acalculous Cholecystitis

Inflammation of the gallbladder can occur in the absence of gallstones. In adults, acute acalculous cholecystitis may appear in: elderly men, those with vasculitis others debilitated with sepsis, burns, trauma or following surgery; and with pregnancy. Biliary stagnation accompanied by occult sludge appears to be a factor. Impaired blood flow to the gallbladder, coagulation factors and prostaglandin may also have roles. Opportunistic infections like cytomegalovirus or cryptosporidia can cause gangrenous cholecystitis in patients who harbor HIV or are immunocompromised such as with bone marrow transplantation. In young children, acute cholecystitis may develop following a febrile illness like that with the Ebstein-Barr virus.

Clinical presentation may differ from acute calculous cholecystitis. The abdominal pain and tenderness are often obscured by the patient's underlying critical condition with seemingly obscure sepsis as the primary feature. Diagnosis is then revealed at laparotomy, but sometimes can be determined preoperatively by non-visualization of the gallbladder on HIDA (although non-visualization is less sensitive here because of the prolonged fast in these often debilitated patients – the resultant viscous bile prevents filling). Here too, ultrasonography is the best imaging procedure yielding: evidence of a thickened gallbladder wall, a pericholecystic cystic fluid collection and/or a positive sonographic Murphy's sign. Perforation, gangrene and empyema are all too frequent complications. The best treatment is prompt cholecystectomy. Prevention is possible in some patients on complete TPN (total parenteral nutrition with no oral intake) following major surgery, trauma or burns. Daily injections of cholecystokinin (CCK) to stimulate gallbladder evacuation can prevent sludge formation and its complication, cholecystitis.

3.2.2. Acalculous Biliary Pain, Chronic Acalculous Cholecystitis and Biliary Dyskinesia

Recurrent biliary-type pain in the absence of gallstones has been attributed to a variety of often overlapping disorders, including chronic acalculous cholecystitis, and gallbladder/biliary dyskinesia, which share symptomatology but differ any pathologic findings in the resected gallbladder. Episodic biliary pain in the absence of demonstrable gallstones accounts for almost 15% of cholecystectomies performed, especially in young women. Ultrasonography-based surveys indicate that this figure may be even higher in the general population. In some, such acalculous biliary pain has been associated with rather modest, albeit nonspecific, gallbladder inflammation: chronic acalculous cholecystitis. The basis has been attributed to a motility disorder, impaired gallbladder evacuation: hence the alternative term "biliary dyskinesia." Relief can follow cholecystectomy but difficulties arise in attempting to make this diagnosis: the symptoms are often not clear-cut (sometimes having coexisting features of the irritable bowel syndrome or non-ulcer dyspepsia). Abnormal gallbladder emptying in response to CCK may be evident on cholescintigraphy but its true value remains unclear.

In others who have undergone a cholecystectomy for recurrent RUQ pain, the origin of the problem has been attributed to sphincter of Oddi dysfunction , either as a motor disorder or hypersensitivity of the sphincter. In many, the pain may represent just one facet of a more diffuse functional gut disorder and/or visceral hypersensitivity or intense spasms of a nearby structure in the right upper quadrant such as the duodenal sweep or hepatic flexure of the colon.

3.3. Cholecystoses

Cholesterolosis consists of deposits of cholesterol esters and triglycerides within the gallbladder wall. Some of the cholesterol deposits may protrude like polyps that can be detected on ultrasound (cholesterol polyps). A rather common histopathological finding discovered post mortem or on ultrasound done for other reasons, cholesterolosis is not associated with any well-defined symptom complex. It has been associated with vague dyspeptic complaints, the irritable bowel syndrome, or ideopathic recurrent right upper quadrant abdominal pain. As cholesterolosis is not thought to cause symptoms, no treatment is warranted.

Adenomyosis is characterized by hyperplasia of the gallbladder mucosa and by deep clefts. Coexisting biliary-type symptoms are generally felt to be incidental, when present.

3.4. Postcholecystectomy Complications
3.4.1. Post-Cholecystectomy Inflammatory Conditions

Bile leaks can occur after laparoscopic cholecystectomy, usually because of either a cystic duct clip that is not secure or from inadvertent transection of a small branch (duct of Luschka) of the right intrahepatic duct that runs through the gallbladder bed on its way to the common duct. The presentation results from bile irritating the peritoneum and causing post-operative pain, sometimes with fever or peritoneal signs. Bile may be evident in the peritoneal drains. Serum bilirubin (reabsorbed after leaking) and liver enzymes are often elevated. Diagnosis comes from a hepatobiliary scan demonstrating the leak and/or by ultrasound showing a biloma (collection of bile). ERCP will confirm the diagnosis and provide therapy byinserting a stent for four to six weeks. The stent decreases resistance across the papilla and so encourages bile to flow into the duodenum, rather than through the leak site. Such leaks often heal in the first few weeks, avoiding re-operation. In 20-30% of patients, another obstructing diagnosis, such as a retained bile duct stone or an ampullary adenoma, coexists.

Strictures can arise after cholecystectomy either from mechanical trauma when attempting to clip the cystic duct or because of focal ischemia. Presentation is post-operative pain and jaundice. Some require re-operation and biliary reconstruction. Endoscopic therapy may be attempted for ligations that are incomplete. Ischemic strictures can present months later, with progressive cholestasis or abrupt jaundice if they are complicated by sludge. ERCP provides the diagnosis and treatment, employing progressive balloon dilatation and stenting. Temporary (removable) covered metal stents can also be used, especially in refractory cases. Strictures may be persistent, necessitating repeated procedures.

3.4.2. Post-Cholecystectomy Syndromes

Cholecystectomy relieves the symptoms of most, but definitely not all patients with biliary calculi. In general, the surgical complications discussed above, such as bile leaks and strictures, are rare and present early.

The *postcholecystectomy syndrome* is a term that primarily refers to pain that returns weeks or years after removal of the gallbladder. A few are experiencing recurrent biliary tract problems such as a retained common duct stone, best investigated with MRCP or EUS. In some patients, a careful history may reveal that the original complaint leading to cholecystectomy may not have been true biliary pain, but rather gastroesophageal reflux, functional dyspepsia or the irritable bowel syndrome. Diagnostic cholangiography using ERCP is generally not recommended in these patients because of the high risk pancreatitis following the procedure.

Sphincter of Oddi dysfunction, though not common, should be suspected when true biliary pain is recurring in the absence of a gallbladder (i.e.; post-cholecystectomy), but no duct pathology can be identified to explain the pain on MRCP or EUS. The basis is increased tone in the sphincter of Oddi that produces recurrent biliary-type pain, often with abnormal liver biochemistries, a dilated bile duct, or even pancreatitis. When clear cut features are present during an attack (typical pain, enzyme changes and a dilated common bile duct, endoscopic sphincterotomy should be considered, as >90% will experience relief of pain. In those with few features, biliary nuclear medicine scanning can show delayed drainage from the biliary system, but its true value in equivocal cases, especially when the duct is not dilated, remains unproven. Sphincter of Oddi pressure measurements (manometry via ERCP showing basal pressures > 40 mmHg) may be the gold standard for sphincter of Oddi dysfunction, but ERCP when performed in such patients is associated with a higher than average post-ERCP pancreatitis rate (5-15%) and thus should be reserved for expert centers.

Some patients following cholecystectomy experience "diarrhea", often with post-prandial urgency. The basis for such diarrhea following removal of the gallbladder likely results from the unmasking of bile salt malabsorption that leads to a cholerrheic (bile salt-related) diarrhea. A nuclear medicine scan for bile using a radiolabeled, synthetic bile salt can assess its absorption in the terminal ileum (SeCAT scan). Bile salt diarrhea should respond to bile acid binding resins like cholestyramine, and empiric trials of this are reasonable.

3.5. Neoplasms of the Gallbladder

Carcinoma of the gallbladder is fortunately uncommon, as its prognosis is extremely poor. Adenocarcinoma is generally cured only when incidentally discovered at cholecystectomy for cholelithiasis. Gallstones are present in most (75%) cases, probably as innocent bystanders rather than as causal agents. The carcinoma risk however is too low to advocate prophylactic cholecystectomy in the many people with asymptomatic gallstones. Conversely, a porcelain gallbladder with calcifications in the wall predisposes to adenocarcinoma and calls for cholecystectomy. Large gallstones (> 3 cm) are also a risk factor for carcinoma, as is primary sclerosing cholangitis.

The clinical features of gallbladder carcinoma consist of abdominal pain, a hard mass in the right epigastrium, jaundice, pruritus and weight loss. Ultrasound and CT scan help define the mass and metastases. Prognosis is grim, as it is common for the cancer to spread. The five-year survival is less than 5%. Therapy is palliative; most are not resectable at presentation unless found incidentally at the time of a cholecystectomy performed for another indication.

Benign tumors of the gallbladder are uncommon. Adenomas are asymptomatic, being detected on ultrasound or found incidentally at surgery. Small masses in the wall of the gallbladder, however, are relatively common findings on ultrasound; when multiple they usually

represent cholesterol polyps or adherent gallstones. If polyps are larger than 1 cm, cholecystectomy is recommended. Routine follow-up (ultrasound) of those <1 cm is controversial.

4. Other (Non-Calculous) Diseases of the Bile Ducts
4.1. Congenital

Fibrocystic disorders: This group of disorders comprises biliary tree maldevelopment. Cystic dilatation and/or fibrosis are due to genetic abnormalities in the remodeling of the ductal plate. The type of disease depends on the part of the ductal plate involved. All, except Caroli's disease, may be associated with polycystic kidney disease. The prognosis usually depends on the extent of renal involvement. The later the presentation, the less significant is the renal component of the syndrome: 90% in perinatal vs. 25% in three- to six-month-old infants.

Caroli's disease (congenital intrahepatic biliary dilation) is a rare condition in which saccular, dilated segments of the intrahepatic bile ducts can lead to stone formation, recurrent cholangitis and/or liver abscesses. Episodes of abdominal pain, fever and jaundice, most commonly occur in childhood or young adult life. About 75% of patients are male; hepatomegaly is common. Cholangiocarcinoma and amyloid can be rare late complications. Cholangiography reveals the irregularly dilated segments of the intrahepatic bile ducts that connect with the main ducts. The common duct is normal. Management is conservative, using antibiotics for infectious complications of the duct system. Endoscopy (or surgery) can remove some stones but does little for the process that affects small bile ducts in the liver. If involvement is unilateral (usually left-sided), partial hepatectomy can be curative. These recurrent episodes of cholangitis can rarely progress to secondary biliary cirrhosis, portal hypertension and eventually cholangiocarcinoma. In such cases, liver transplantation may become necessary.

Congenital hepatic fibrosis frequently accompanies Caroli's disease; the combination is termed *Caroli's syndrome*. This phenomenon perhaps reflects a developmental defect of the small interlobular ducts. Congenital hepatic fibrosis presents as portal hypertension with esophageal varices in children. Liver biopsy is diagnostic, revealing broad bands of fibrous tissue entrapping bile ducts.

Choledochal cyst is an uncommon congenital dilation of a portion of the common bile duct that develops because of an uneven proliferation of the duct epithelial cells. The cyst wall consists of fibrous tissue, lacking epithelium or smooth muscle. More than 50% of cases are associated with an anomalous pancreaticobiliary junction, due to an arrest of the normal descent of this junction from outside the duodenum to within the duodenal wall in the last eight weeks of gestation. A long common pancreaticobiliary channel (> 15 mm) may allow pancreatic juice reflux in the bile duct, causing distal stricturing and thinning of the bile duct proximally, at least in some cases. Choledochal cysts have been classified into subtypes dependent upon site, most commonly as a fusiform dilatation of the extrahepatic bile duct, but also as a sidewall diverticulum or even bulging as a sac into the duodenum. Presentation may be as cholestasis in infants (if the cyst and/or stricture is complicated by sludge), as an abdominal mass, or rarely, as an acute abdomen if the cyst bursts and causes bile peritonitis. The cysts can be quite large: 2-8 cm in size and having up to 8 L of dark brown fluid. Later in life, they present as intermittent jaundice, biliary pain and cholangitis. Chronic obstruction rarely can lead to biliary cirrhosis and

the development of ductal carcinoma (cholangiocarcinoma). Diagnosis is provided by ultrasound or CT scan and verified by endoscopic cholangiography. Because of the risk of malignancy, either related to the cyst itself or to the abnormal pancreaticobiliary junction, a radical excision with hepaticojejunostomy is preferred. This also helps reduce the postoperative risk of stricturing and stone formation when the bile duct is surgically attached to the intestine.

Alagille's syndrome is a marked reduction in intrahepatic (actually interlobular) bile ducts. Although it is believed to be congenital, being inherited in an autosomal dominant pattern, presentation may be as a neonatal jaundice or as cholestasis in older children. There are associated triangular facies, cardiovascular anomalies (e.g., pulmonary artery stenosis) and vertebral body abnormalities. A mutation in the JAG1 gene is found in 70% of cases. Outcome is variable, depending upon the attendant anomalies and the severity of the liver disease.

Biliary atresia is a common cause of neonatal cholestatic jaundice. Although congenital (appearing at birth), it is not inherited. Complete absence of the extrahepatic bile ducts reflects either an arrest in remodeling of the ductal plate in utero or, more probably, an inflammatory destruction of the formed bile ducts during the postpartum period. An initial viral injury may initiate the epithelial injury that then progresses by an immune-mediated sclerosing process, abetted by bile salt leakage that adds detergent damage. The resultant sclerosing inflammation obliterates both the intra- and extrahepatic bile ducts, resulting in profound cholestasis and then secondary biliary cirrhosis. Severe cholestasis presents in the neonatal period. The stools are pale; the urine is dark and devoid of urobilinogen. Chronic cholestasis then leads to steatorrhea, skin xanthomas, bone disease and failure to thrive. Surgery is usually necessary to confirm the diagnosis and attempt some form of biliary drainage. In some, existence of a patent hepatic duct or dilated hilar ducts allows correction of the obstruction by anastomosis to the small intestine (e.g., a Roux-en-Y choledochojejunostomy). More common is an absence of patent ducts; dense fibrous tissue encases the perihilar area and precludes conventional surgery. Such obliteration of the proximal extrahepatic biliary system requires the Kasai procedure. A conduit for biliary drainage is fashioned by resecting the fibrous remnant of the biliary tree and anastomosing the porta hepatis to a roux-en-Y loop of jejunum. With either surgery, most children eventually develop chronic cholangitis, hepatic fibrosis/cirrhosis and portal hypertension. When the child is larger, hepatic transplantation dramatically improves the prognosis. Liver transplantation becomes necessary in 50% by 2 years of age, 80% by 20 years.

Other causes of neonatal cholestasis can be attributed to hepatocellular transport defects, best exemplified by familial intrahepatic cholestatic syndromes.

Von Meyenberg's complexes are biliary microhamartomas. They are thought to arise from a maldevelopment of the ductal plate. These small, multiple cysts are usually asymptomatic though potentially complicated by cholangiocarcinoma. They are usually only treated if symptomatic.
.

4.2. Inflammatory
4.2.1. Cholangitis

Cholangitis is any inflammatory process involving the bile ducts, but common usage implies a bacterial infection, usually above an obstructive site (usually a bile duct stone). The presence of bacteria in the biliary tree plus increased pressure within the system results in severe

clinical features of cholangitis (*suppurative/bacterial cholangitis*). Any condition producing bile duct obstruction is likely to cause bacterial infection of bile. Most commonly, this takes the form of a common duct stone (Section 2.3), stasis in a congenital biliary cyst (Section 4.1), a parasite residing in the ducts (*Clonorchis sinensis, Opisthorchis viverrini* or *Fasciola hepatica*), an occluded biliary stent, or extrinsic compression from a diseased papilla or pancreas. Whenever the duct has been contaminated via an ERCP/stent, there is an intermediate risk of cholangitis.

A less likely cause of infection is a stricture (such as a neoplasm) that has not been contaminated by a stent; only 10-15% of malignant biliary obstructions are associated with infection at presentation. The difference relates to the slowly progressive obstruction of non-contaminated strictures versus the intermittent blockage with a stone or acute blockage of as stent within a duct that has been colonized by bacteria via the stent. Such intermittent blockage allows retrograde ascent of bacteria: the stone or stent acting as a nidus for infection. The bacteria ascend the biliary tree (hence the term "ascending cholangitis"), but may also enter from above via the portal vein or from periductular lymphatics. In acute bacterial cholangitis, particularly if severe, the classical Charcot's triad of intermittent fever and chills, jaundice and abdominal pain may be followed by septic shock. Most cases are less severe and life-threatening; jaundice may be absent. Mild cases may respond to antibiotics and conservative measures. Investigation and decompression of the biliary system are mandatory in all patients, whether by ERCP, PTC or surgery. The duration of antibiotics needed after successful biliary drainage can be as short as three to five days, unless bacteremia coexists.

4.2.2. Sclerosing Cholangiopathies
Primary sclerosing cholangitis:

Primary sclerosing cholangitis (PSC) is a chronic cholestatic syndrome, distinguished by progressive inflammation and fibrosis of the intra- and extrahepatic bile ducts. PSC is uncommon (incidence of 0.9 per 100,000). It predominantly affects men aged 35-50 years. The entity may appear either alone (20%) or in association with inflammatory bowel disease (80%), particularly ulcerative colitis and less commonly, Crohn's colitis. PSC may precede inflammatory bowel disease (especially ulcerative colitis) and runs a separate course, not being cured by colectomy. The basis for the patchy scarring (sclerosis) that leads to fibrotic narrowing and eventually obliteration of the bile ducts is unknown. In a genetically predisposed individual, biliary epithelial damage likely begins with exposure to an infectious agent and/or enterohepatic toxin. In inflammatory bowel disease with defective intestinal permeability, this might originate from transmigration of bacteria and toxins. An autoimmune process might then perpetuate the attack.

PSC is insidious; most patients are asymptomatic at presentation, particularly in those with inflammatory bowel disease who are identified by having cholestatic liver enzymes on routine testing. Clinical symptoms begin with fatigue and pruritus. Progression leads to jaundice, weight loss, chronic cholestatic features. Complications include episodes of bacterial cholangitis with upper abdominal pain, fever and worsening cholestasis. Secondary biliary cirrhosis with portal hypertension supervenes and progressive liver failure. Those with ulcerative colitis have a heightened risk of colon and hepatobiliary cancers.

The liver biochemistry is cholestatic with elevated alkaline phosphatase and GGT. Serology often includes antoantibodies like ANA, SMA and p-ANCA (80% of cases) at low levels, but not antimitochondrial antibodies, an important distinction from primary biliary cirrhosis. Diagnosis requires high-resolution bile duct imaging to show diffuse strictures and

dilation of both the intra- and extrahepatic bile ducts. MRCP is quite accurate for PSC. ERCP is reserved for equivocal cases, or for biliary intervention: stones, sludge and a dominant biliary stricture. Liver biopsy is not usually necessary except for difficult cases: 1. Small-duct PSC - these have a sclerosing cholangitis with the clinical and biochemical features of PSC, but have a normal cholangiogram (as small ducts are involved). Some will progress to classic (large duct) PSC; and 2. Autoimmune hepatitis overlapping with PSC.

Management includes that for chronic cholestasis: treating the pruritus with bile-salt binding resins (cholestyramine) and using ERCP to dilate any dominant strictures; preventing metabolic bone disease (calcium, vitamin D) and nutritional management of steatorrhea including use of fat-soluble vitamins. Therapeutic trials of corticosteroids, immunosuppressive agents (for the presumed immunologically mediated inflammatory process), ursodeoxycholic acid (to theoretically displace any toxic bile acids and be anti-inflammatory) and proctocolectomy in patients with inflammatory bowel disease have all failed to change outcomes. As some patients may be asymptomatic for a decade, only careful observation is probably warranted early on. Recurrent bacterial cholangitis requires antibiotics and sometimes ERCP to remove extrahepatic sludge/stones. Extrahepatic "dominant", large-duct strictures, associated with symptoms or significant cholestasis warrant ERCP balloon dilation, generally avoiding stenting because of the risk of contamination of upstream, poorly draining biliary segments.

Prognosis from diagnosis to death or liver transplantation is about 10 years. The development of jaundice, intractable pruritus and features of cirrhosis (ascites, portal hypertension with esophageal bleeding) are indications for liver transplantation (with a Roux-en-y choledochojejunostomy). The outcome is quite good with a 5-year survival exceeding 80%. PSC recurs in 20%. Some 10-15% of patients develop cholangiocarcinoma, creating a diagnostic challenge. Unexplained weight loss, a rising CA19-9 serum tumor marker (e.g. >100IU), or recent worsening of cholestasis should raise suspicion. MRCP imaging and/or ERCP with biliary brushings or other sampling/cholangioscopy are then warranted. . The development of cholangiocarcinoma prior to transplantation has a poor prognosis; the cancer progresses with immunosuppression, and is generally a contraindication to transplantation.

Other Sclerosing Cholangitides

Secondary sclerosing cholangitis causes diffuse stricturing. It complicates biliary obstruction from a common duct stone, ischemia, biliary stricture or cholangiocarcinoma, or some HIV-related infections. An infiltrative process (e.g., diffuse liver metastases, lymphoma, prominent regenerative nodules, and sarcoidosis) can also give a beaded appearance to the intrahepatic ducts that can mimic PSC.

IgG4-associated cholangiopathy is an autoimmune, steroid-responsive, sclerotic process manifest by IgG-4-positive plasma cell infiltration producing segmental stricturing in the larger bile ducts. Half of the strictures are confined to the intrapancreatic portion of the bile duct. The condition was originally described as a variant of autoimmune pancreatitis (AIP) and can be associated with various other autoimmune diseases. It is most common in older males, typically 60 years. IgG4-related cholangitis differs from PSC in several other ways: not commonly associated with inflammatory bowel disease; characteristically has elevated serum IgG-4 levels, and the strictures respond to corticosteroids (e.g. prednisone 30-40mg/d for 4-6 weeks). Hence, serum IgG-4 should be assessed in those with suspected PSC (which is not steroid-responsive).

To aid the diagnosis, IgG4 immunostaining tissue can be obtained from the ducts, ampulla or pancreas (e.g. by EUS-guided core) in serology-negative cases. Characteristic changes in the pancreas and duct wall can be seen on EUS and ERCP. Recurrence after treatment is common. Associated autoimmune pancreatitis with inflammatory masses, and associated weight loss, can sometimes make this difficult to differentiate from malignancy.

4.3. Neoplasia

Benign tumors (adenomas, papillomas, cystadenomas) are rare causes of mechanical biliary obstruction. Ampullary adenomas can be associated with colonic polyposis syndromes. Localized adenomas of < 2 cm are amenable to endoscopic removal. Ampullary adenocarcinomas should be considered for a Whipple's pancreaticoduodenectomy.

The most common malignant stricture of the bile duct is due to invasion from to pancreatic cancer.

Cholangiocarcinoma, the most frequent primary biliary tract malignancy, is rather uncommon in the Western world. Predisposing factors are chronic parasitic infestations of the biliary tract (e.g., a liver fluke, such as *Clonorchis sinensis* or *Opisthorchis viverrini*), congenital ectatic lesions (anomalous pancreaticobiliary junction, Caroli's disease, choledochal cyst) and primary sclerosing cholangitis.

Painless jaundice is the hallmark presentation, but the presentation is varied. Cholestasis and weight loss eventually develop. There may be a deep-seated, vague discomfort - a feeling of fullness localized in the right upper quadrant of the abdomen. Indeed, cholangitis is uncommon (10-15%) if biliary manipulations, such as an ERCP-placed stent, have not been performed. A distended, non-tender gallbladder may rarely be palpated, feeling like a small rubber ball, if the common duct is obstructed below the insertion of the cystic duct ("Courvoisier's sign"). Obstruction produces dilation of the biliary tree that can be readily detected on ultrasound or CT scan. MRCP/ERCP often shows an irregular, shouldered (as opposed to smoothly tapering) stricture; EUS shows bile duct wall thickening or a mass centered on the duct or at the liver hilum. A discrete mass is often not appreciated on cross-sectional imaging (CT/MR). An elevated prothrombin time/INR can occur due to cholestasis and anorexia, and needs to be corrected prior to ERCP/PTC. Tissue diagnosis is problematic. ERCP brushings for cytology have a relatively low yield for malignant cells (<40%). EUS and fine needle aspiration can help, especially in hilar tumors, or with the tumor is >2cm (yield > 70%). This slow-growing tumor unfortunately presents late.

Surgery for distal bile duct tumors is similar to a head of pancreas cancer (i.e. a Whipple pancreatoduodenectomy). For hilar/intrahepatic tumors, surgical decisions are more complicated and depend on stage (like vascular and bilateral liver involvement). If non-invasive imaging reveals a resectable non-hilar lesion in a young surgical candidate, it may be reasonable to go straight to surgery avoiding stenting, but generally a tissue diagnosis is pursued preoperatively in most patients. Palliation of distal tumors using biliary stents placed across strictures helps improve quality of life via alleviating jaundice, pruritus. Plastic stents are removable/exchangable but occlude after an average of 3-4 months, whereas self-expandable metal stents (both removable and non-removable varieties now available) can last longer (6-12 mos), but are much more costly (5-10 times).

Hilar tumors are managed differently (both surgically and endoscopically) and should be suspected when the characteristic painless jaundice of cholangiocarcinoma occurs in the presence of intrahepatic biliary dilatation, but without extrahepatic biliary dilatation. MRCP is

non-invasive and quite accurate at staging these tumors (Bismuth classification) and determining their resectability. If not resectable, the MRCP also determines the feasibility of endoscopic/percutaneous drainage. Only 30% of the biliary tree needs be drained to alleviate jaundice. Draining one lobe is often sufficient for palliation although occasionally both sides may require drainage, especially if both sides are contaminated with dye at a procedure, or if cholangitis develops after stenting one side.

Chapter 32: Pancreas
*F. Habal, G. Gaisano, S. Carpentier and
A. B. R. Thomson*

1. Aantomy

The pancreas is located retroperitoneally in the upper abdomen overlying the spine and adjacent structures, including the inferior vena cava, aorta and portal vein and parts of their major tributaries. Its retroperitoneal location makes the pancreas relatively inaccessible to palpation. The head and unci—nate process lie within the curvature of the duodenum, while the body and tail extend to the hilus of the spleen. The arterial supply of the pancreas is from the major branches of the celiac artery, including the splenic and gastroduodenal arteries, and the superior mesenteric artery, as well as an arborization of smaller branches (i.e., the superior and inferior pancreatico- duodenal arteries) arising from these main arterial trunks. Venous supply comes from the superior mesenteric and splenic veins, which join together to become the portal vein (Figure 1). The pancreas does not have a capsule, and therefore pancreatic cancer often invades vascular structures, particu—larly the superior mesenteric vessels located directly posterior to the angle between the head and body of the pancreas. Nervous supply comes from parasympathetic branches of the vagus nerve, which provide a major secre—tory stimulus, and the sympathetic branches of the intermediolateral column of the thoracic spinal cord. Pain fibers are believed to accompany these sympathetic branches, which overlap those supplying the posterior abdomi—nal wall structures, and which thereby account for the back pain experienced with pancreatic diseases.

The exocrine pancreas is drained by two duct systems. The major duct (duct —of Wirsung) originates from the embryonic ventral pancreas and traverses the pancreas from the head of the pancreas to the tail. At the head it turns ~~downward~~ caudal and ~~backward~~ posterior to approach the infraduodenal portion of the common bile duct at the ampulla of Vater. The ampulla's opening is regulat—ed by the sphincter of Oddi. The minor duct (duct of Santorini) originates from the embryonic dorsal pancreas, which supplies part of the anterior head, and enters the duodenum as a separate minor ampulla several centimeters above the ampulla of Vater. The minor duct fuses with the major duct in > 90% of people. I, ~~but i~~n the minority, a lack of fusion of these two ducts results in the drainage of the head and body of the pancreas into the minor duct at the smaller ampulla, causing relative outflow obstruction. This anatomical variation, called pancreas divisum, is believed by some to be a cause of pancreatitis.
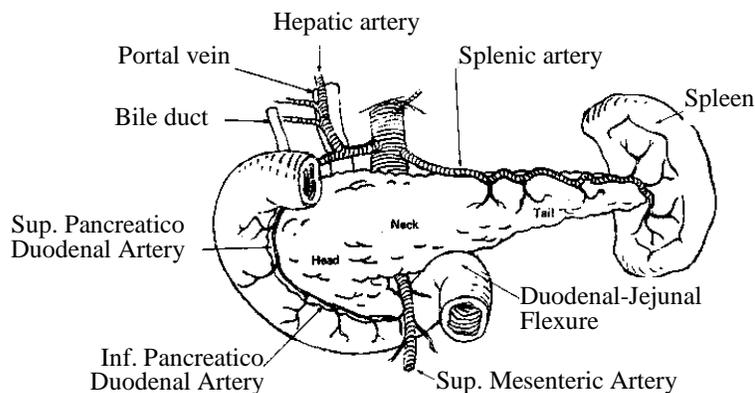
Figure 1. Relationships and blood supply of the pancreas.

The pancreatic tissue consists of endocrine and exocrine portions. The islets of Langerhans are islands of cells scattered throughout the pancreas. The majority of the islet cells are beta cells, which secrete insulin, whereas the non-beta cells secrete glucagon, pancreatic polypeptide and somato‑statin. The exocrine portion (Figure 2) accounts for over 80% of the pancreatic mass~~., and is~~It is composed of primarily 1) acinar cells that secrete digestive enzymes and 2) centroacinar and ductal cells that secrete fluid and electrolytes, particularly bicarbonate.

Pancreatic lobule
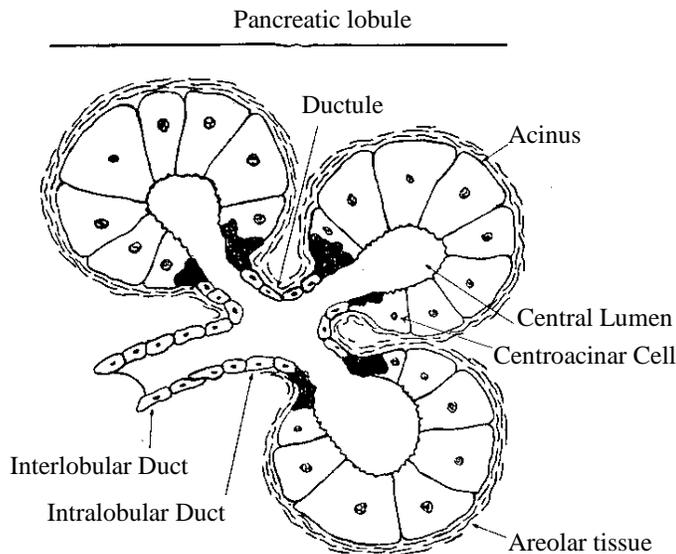
Figure 2. Schematic representation of acinar structure of exocrine pancreas.

2. Physiology

Pancreatic acinar and ductal secretions are regulated by neural and endocrine stimuli. The major peptide hormones stimulating acin~~ari~~ar and ductal cells, respectively, are cholecystokinin (CCK) and secretin. Some peptide hormones~~, including~~ such as somatostatin and pancreatic polypeptide, *inhibit* secretion.

2.1 Enzyme Secretion

The acinar cells secrete about 20 digestive enzymes, the vast majority of which ~~are in their inactive forms. These enzymes~~are proenzymes later ~~become~~ activated in the intestinal lumen ~~to digest ingested proteins, carbohydrates and fat.~~ The pancreas has a great capacity ~~to secrete these enzymes~~for enzyme secretion, such that at least 90% of the gland ~~has to~~must be destroyed before clinically significant maldigestion ~~of nutrients~~, leading to malnutrition, would be observed.

The pancreatic acinar cell secretes proenzymes, and ~~mainly~~ enzymes ~~whose purpose is to~~that digest proteins, carbohydrates and lipids. Of these, amylase, and lipase are of particular clinical relevance. Other secretory products include ribonucleases, ~~anti~~proteases and glycoprotein-2 (GP-2). All the digestive enzymes are packaged in zymogen granules within the acinar cell in their inactive proenzyme forms, except for amylase and lipase. The digestive

enzymes synthesized in the rough endoplasmic reticulum are packaged with—in the Golgi apparatus and specifically targeted

into the zymogen granules, which undergo a series of maturation steps involving condensation of the protein contents and shedding of excess membranes of the secretory vesicle. Each zymogen granule becomes very densely packed with digestive enzymes (they are called "dense core granules") and lodges at the apical pole of the acinar cell, waiting for a stimulus to induce exocytotic fusion at the apical plasma membrane, which releases the granule's contents. These vesicular transport processes could be blocked in a manner that causes fusion of the zymogen granule with lysosomes, allowing lysosomal hydrolytic enzymes to activate the digestive enzymes, or alternatively, causes pathologic fusion of the zymogen granule with the lateral side of the acinar cell. These patholog~~ic~~ic processes ~~result in intracellular and interstitial digestion, respectively, resulting in cellular damage and cellular death i.e., pancreatitis.~~ ~~This is currently believed to be the earliest initiating cellular process causing clinical acute pancreatitis.~~have been hypothesized to play a role in the development of acute pancreatitis. Certainly, it is widely accepted that the inappropriate/uncontrolled activation of trypsin within the acinar cell is one of the most important pathological steps in acute pancreatitis.

Glycoprotein-2 (GP-2), which plays a role in stabilizing the zymogens, has the tendency to~~of~~ form~~ing~~ protein plugs when excreted in excess into the ducts. These protein plugs serve as a nidus for calcium deposition and result in pancreatic ductal obstruction and smoldering inflammation leading to fibrosis and atrophy. This mechanism has been implicated in alcohol-induced chronic pancreatitis. A recently discovered relationship between ductal bicarbonate secretion and acinar GP-2 secretion also implicates GP-2 in chronic pancre~~-~~atitis of patients with cystic fibrosis.

Under normal conditions, u~~U~~pon release of ~~the~~ digestive proenzymes into the intestinal lumen, trypsinogen is activated by enterokinase to active trypsin, which in turn activates all the other ~~enzymes~~ digestive enzymes. (Figure 3). ~~–~~Appropriate conditions, most importantly an alkaline pH brought about by the ductal bicarbonate secretion, should be present for ~~the~~ digestive enzymes to be active. The optimal pH of these digestive enzymes ranges from 7 to 10.
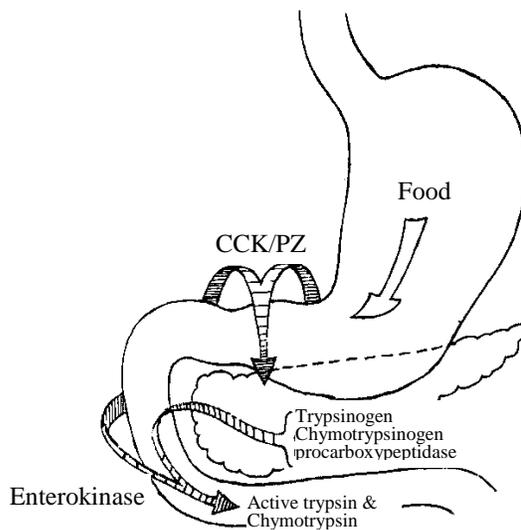
Figuer 3. Role of cholecystokinin (CCK), ~~/~~pancreozymin (PZ) and ~~of~~enterokinase activation in pancreatic secretion.

~~T~~The proteases are components of pancreatic secretions that break down specific protein peptide bonds to form amino acids. Endopepsidases such as trypsin and chymotrypsin cleave peptide bonds in the middle of the protein ~~, called endopeptidases (trypsin and chymotrypsin), or at the carboxyl end~~whereas (carboxypeptidases act at the carboxyl terminus. The essential amino acids liberated by these mechanisms effect pancreatic secretion and upper GI motility.~~A and B). Amylase hydrolyzes starch to maltose, maltotrioses and dextrins.~~

Importantly, both amylase, and lipase, are secreted into the small intestine in their active forms. Amylase hydrolyzes starch to maltose, maltotrioses and dextrins. The effective action of lipase is more complex than that of either pancreatic proteases and amylase. This complexity accounts for the relatively low survival of lipase among the digestive enzymes. In fact, in pancreatic exocrine insufficiency, frequently only fat maldigestion is evident. Among these enzymes, lipase has the highest optimal pH (> 8) requirement, is most susceptible to inactivation by low pH, and requires a cofactor, colipase, for its optimal activity. Lipase acts at the oil–water interface of fat droplets. Its action results from emulsification of the food bolus, which is effected by the churning motion of the stomach and the action of bile acids. The bile salts then solubilize the fat into micelles. Colipase binds to lipase , stabilizes it, and prevents it from being inhibited and removed from the oil–water interface by bile salts. Perturbation of any of these processes will adversely affect the action of lipase on fats.

Acinar Cells — Enzyme Secretion

Centroacinar Cells — Secretin-Stimulated Secretion: Na^+, K^+; Cl^-, HCO_3^-; H_2O

Extralobular Ducts — Secretin-Stimulated Secretion: Na^+; HCO_3^-; H_2O

Exchange: HCO_3^-; Cl^-

Main Duct — No Secretion or Exchange

HCO_3^-	Cl^- mEq/L
52	112
56	108
92	73
108	56
118	46

~~The effective action of lipase is more complex than the proteases and amy lase. This complexity accounts for the relatively low survival of lipase among the digestive enzymes. In fact, in pancreatic exocrine insufficiency, frequently only fat maldigestion is evident. Among these enzymes, lipase has the highest optimal pH (> 8) requirement, is most susceptible to inactivation by low pH, and requires a cofactor, called colipase, for its optimal activity. Lipase acts at the oil water interface of fat droplets. Its action results from emulsification of the food bolus, which is effected by the churning motion of the stomach and the action of bile acids. The bile salts then solubilize the fat into micelles. Colipase binds to lipase to stabilize the lipase in a manner that~~

prevents lipase from being inhibited and removed from the oil-water interface by bile salts. Perturbation of any of these processes will adversely affect the action of lipase on fats.
The effective action of lipase is more complex than the proteases and amy- lase. This complexity accounts for the relatively low survival of lipase among the digestive enzymes. In

Figure 4. Secretion by centroacinar cells and by cells of the extralobular ducts of the pancreas. Chloride concentrations (right) were determined on fluid collected by micropuncture, and the bicarbonate concentrations were inferred from the fact that the fluid is isotonic. These data are for the cat pancreas, but other species seem to be similar.

Source: Adapted from Lightwood R, Reber HA. Micropuncture study of pancreatic secretion in the cat. *Gastroenterology* 1977;72:61.

2.2 Bicarbonate Secretion

The ductal and centroacinar cells ~~secrete about 1-2 L of~~contribute to a total secretion of 2.5 L of pancreatic juice per day. The pancreatic juice is isotonic with a pH of 8–9. The anion concentra—tion exceeds 150 mEq/L, consisting of Cl^- and HCO_3^- (Figure 4). At high flow rates such as after a meal, HCO_3^- secretion predominates over Cl^- secretion, and the reverse is true at low flow rates. This change in HCO_3^- / Cl^- ratio is effected by a ductal plasma membrane HCO_3^-/ Cl^- exchanger, which is activated by secretin-mediated cAMP pathways. The HCO_3^- is necessary to neutralize the acidic (pH< 2) gastric chyme entering the duodenum to a pH level (> 6) that is optimal for enzymatic digestion.

2.3 Regulation of Pancreatic Secretion

There are two patterns of pancreatic secretion. The first pattern is *basal secretion,* which is punctuated every 1 or 2 hours by bursts of increased bicar—bonate and enzyme secretion that last 10 to 15 minutes. The second pattern is the *postprandial stage*, which results from a complex interaction of neural and hormonal mechanisms.

The postprandial stage is divided into three phases. The *cephalic phase* occurs in response to the sight, smell and taste of food and is mediated by the vagus cholinergic nerves. Cholinergic stimulation has a primary stimulatory effect on acinar enzyme secretion, and a secondary potentiating effect on secretin-mediated ductal HCO_3^- secretion. The *gastric phase* occurs in response to distention of the stomach, which affects vagova—gal neural reflexes and stimulates the release of gastrin. Both vagal reflexes and gastrin stimulate pancreatic enzyme secretion and gastric parietal cell acid secretion.

The *intestinal phase*, which is initiated in the duodenum, accounts for the major stimulation of both enzyme and bicarbonate secretion. The pres—ence of products of fat and protein digestion in the duodenum stimulates the release of CCK, which in turn stimulates acinar enzyme secretion. When gas—tric acid entering the duodenum decreases the duodenal pH to < 4.5, secretin is released, which stimulates ductal bicarbonate secretion. CCK acting via calcium pathways and secretin acting via cAMP pathways potentiate each other's effects on enzyme and bicarbonate secretion. Vasoactive intestinal polypeptide (VIP), like secretin, also acts on cAMP pathways to stimulate bicarbonate secretion, and is present and released at vagal nerve endings.

As the chyme reaches further into the small intestine, a number of hor—mones are released which are capable of inhibiting both basal and stimulated pancreatic secretion, and therefore serve as feedback inhibitory mechanisms on enzyme and bicarbonate secretion. These hormones, including pancreatic polypeptide (PP), peptide YY, glucagon, and somatostatin, ~~,~~ are released not only by the small intestine, but also by the stomach and pancreatic islets, ~~which therefore indicate~~ reflecting the complexity of feedback inhibitory pathways~~. These hormones include pancreatic polypeptide (PP), peptide YY, glucagon, somato—statin and other hormones~~ .

3. Pancreatic Function Test

The diagnosis of pancreatic insufficiency is ~~quite evident in the presence of the~~strongly suggested by the clinical triad of pancreatic calcification, steatorrhea_and, less commonly, diabetes.

Pancreatic calcification along with other structural abnormalities of the pancreas, including pancreatic atrophy and ductal ~~dilation~~irregularities, can be diagnosed by radiological imaging (plain x-ray, ultrasound and computerized tomography [CT scan], MRI/MRCP or endoscopic retrograde cholangiopancreatography (ERCP). These radiological tests demonstrating characteristic structural abnormalities of the pancreas, coupled with steatorrhea and or diabetes, are ~~largely~~so strongly suggestive of pancreatic insufficiency that often a clinican will not proceed to functional testing of the gland itself for diagnosis. ~~sufficient to diagnose pancreatic diseases particularly chronic pancreatitis, which makes it unnecessary in the vast majority of cases to proceed to functional testing.~~

Steatorrhea resulting from fat malabsorption has typical clinical features (foul-smelling floating stools, oil droplets). It ~~) and~~ appears earlier than protein malabsorption (azotorrhea) in pancreatic exocrine insufficiency, because of the low survival of lipase. Nonetheless, development of steatorrhea and azotorrhea requires the destruction of at least 90% of the pancreas.

Diabetes is less common in pancreatic diseases, since the islets are remarkably resistant to damage during the inflammatory process. However, when diabetes is present, it follows a more brittle course, since the nonbeta cells producing the counter-regulatory hormones glucagon and somatostatin are also affected.

~~Over~~Pancreatic function tests were initially divised for diagnosis of pancreatic dysfunction. They are now used with more frequency in the research realm. They ~~the years, pancreatic function tests have been devised not only as a diagnostic tool, but more frequently as research tools. These pancreatic function tests~~ ~~may~~ can be divided into two main groups: direct or indirect tests requiring ~~(~~duodenal intubation~~.)~~ and ~~indirect~~non-invasive, indirect tests. (Table 1). Of the pancreatic function tests, the direct invasive tests are the gold standard.

Table 1. **Exocrine pancreatic function tests**

~~I~~Direct invasive intubation tests
CCK/secretin stimulation
Lundh meal
ERCP and pancreatic aspiration

~~N~~Indirect noninvasive tests
Stool fats and nitrogen
Stool trypsin and chymotrypsin
Breath tests
Oral function tests (bentiromide test and pancreolauryl test)

Blood determination
Trypsinogen
Lipase
Pancreatic amylase

Adapted from: Pandol SJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006; page 1197-1199; and 2010, page 928.

3.1 ~~Direct Tube~~Intubation Tests

Comment [SC3]: I changed the heading because the Lundh meal is considered by some to be an "indirect" test despite its invasive nature

"T Tube"/Intubation tests require an oroduodenal tube positioned at the level of the ampulla of Vater to aspirate pancreatic secretion in response to stimuli, including a specific (Lundh) meal or intravenous administration of secretin, with or without CCK. These tests are based on the principle that as pancreatic flow increases with stimulation, there is a progressive increase in bicarbonate con centration (> 80 mEq/L) and a corresponding decrease in chloride concentra- tion. When CCK is infused in conjunction with these tests, trypsin secretion can also be measured. This hormonal stimulation (secretin-CCK) test is believed to be the most sensitive

(> 90%) pancreatic function test. The Lundh test meal, although slightly less sensitive, is more physiologic since it also assesses the normal release of CCK and secretin in response to a meal con—taining protein, fat and carbohydrates. However, the accuracy of the Lundh test is affected by small bowel mucosal disease, rate of gastric emptying and surgical interruption of the gastroduodenal anatomy. Neither test is frequently used because of their disadvantages, including the prolonged (2–3 hours) and unpleasant intubation, and the difficulty of accurate tube positioning. They are therefore not widely available.

Finally, cCannulation of the pancreatic duct during ERCP has been combined with direct stimulation of the pancreas to. This technique allows the measurement of pure pancreatic juice secretion uncontaminated by biliary or intestinal secretion.s, Tbut this method is possibly nohas not been shown to be more sensitive than other tests in the diagnosis of pancreatic diseases.

3.2 Indirect Pancreatic Function (Tubeless) Tests

The standard indirect pancreatic function test is the 72-hour fecal fat determi—nation. Here, tThe patient is placed on a 100 g/day fat diet and the stool is collected daily for three days. Individuals with normal pancreatic function excrete less than 7% of the total amount of fat ingested, whereas those with pancreatic exocrine insufficiency excrete more than 20%. Only a few other conditions, such as extensive small bowel mucosal disease and short bowel syndrome, could cause such a degree of fat malabsorption, such as very extensive small bowel mucosal disease and short bowel syndrome. The major drawbacks ofto stool fat estimations are the lack of specificity and the inconvenience of collecting and analyzing the specimens. Measurements of stool nitrogen and stool chymotrypsin have not proved superior to fecal fat determinations.

Attempts to screen for steatorrhea with less offensive tests (such as urine oxalate levels, ^{14}C-triolein/^{3}H-oleic acid assimilation test, and tripalmitate or palmitic acid breath tests) are promising but not generally accepted. (which test is the rice flour test referring to? Could we delete the rice-flour referral?)

Two oral function tests are available for assessing pancreatic functions: the benitromide test and the pancreolauryl test. The bentiromide test is a urinary test that directly determines pancreatic chymotrypsin secretion. Bentiromide (N-benzoyl-L-tyrosyl-p-aminobenzoic acid [NBT-PABA]) is given orally, and hydrolyzed by chymotrypsin to release PABA. PABA is absorbed by the intestinal mucosa, conjugated by the liver, and excreted in the urine. Fifty percent of the PABA ingested should be recovered in the urine during a six-hour urine collection in normal subjects; less than this indicates pancreatic exocrine insufficiency. Intestinal mucosal, liver and kidney diseases under—standably adversely affect the accuracy of the bentiromide test; m. Measuring plas—ma levels of PABA could circumvent the problem. A number of medicines can also interfere with urine measurement of free PABA, including acetaminophen, sulfonamides and thiazide diuretics.

The pancreolauryl test, using fluorescein dilaurate, has been extensively evaluated in Europe. However, it can detect only severe pancreatic insuffi—ciency and is therefore rarely used.

Chronic pancreatitis may give rise to an abnormal Schilling test, but rarely causes clinical B_{12} deficiency. Vitamin B_{12} is initially bound to an R factor present in saliva, which stabilizes B_{12} in acidic gastric pH. Pancreatic enzymes release the R factor from B_{12} to allow B_{12} to bind to the intrinsic factor secreted by the stomach, which is required for B_{12} absorption at the terminal ileum.

Comment [SC4]: Nitrogen? Does this mean the fecal elastase test?

Formatted: Not Highlight

3.3 Miscellaneous Tests

Differentiating pancreatic carcinoma from chronic pancreatitis can at times be difficult. Many tests have been described to aid diagnosis, but none are of proven value. Assay of carcinoembryonic antigen (CEA) in serum or from pure pancreatic juice obtained during ERCP has not proved to be a useful discriminator. The pancreatic oncofetal antigen has proved to be of uncertain significance. Serum galactosyl II transferase activity has recently been shown to be a reasonably specific indicator of pancreatic carcinoma in some patients. A sophisticated assay, it is unlikely to be suited to widespread use.

Trypsinogen, a proteolytic proenzyme, is exclusively produced in the pancreas. This enzyme can be detected by radioimmunoassay. It is elevated during an attack of pancreatitis and in renal failure, and is decreased in severe pancreatic insufficiency, cystic fibrosis and insulin-dependent diabetes without exocrine insufficiency. The levels of trypsinogen in cystic fibrosis decrease with age if the pancreas is involved. Low levels are found in about 60% of patients with pancreatic insufficiency. Patients with pan—creatic insufficiency who have ongoing inflammation may have normal or raised levels. This fact, in addition to low levels in non–insulin-dependent diabetes, casts some doubt on the usefulness of this test in diagnosing pancreatic insufficiency. It may be useful in patients with steatorrhea that is due to nonpancreatic causes.

Table 2. Causes of elevated serum amylase/lipase

- GI causes
  - Small bowel obstruction
  - Intestinal ischemia
  - Bowel perforation
  - Cholecystitis
  - Salivary gland disease, e.g. mumps
  - Peptic ulcer disease with penetration
  - Pancreatic cancer
  - Pancreatic trauma/surgery
  - Cystic fibrosis
  - Celiac disease
  - Appendicitis
  - Pancreatitis
  - Liver disease

- Non-GI causes
  - Tubo-ovarian disease, e.g. fallopian tube inflammation (salphingitis), ectopic pregnancy
  - Pregnancy
  - Renal failure
  - Diabetic ketoacidosis
  - HIV infection
  - IgA deficiency
  - Anorexia, bulimia
  -
  - Neoplasia

Adapted from: Vissers RJ, et al. *J Emerg Med* 1999;17(6):1027-37.

3.4 Tests Suggestive of Active Disease

When faced with a patient with hyperamylasemia, it is necessary to exclude disease involving many organs other than just the pancreas (Table 2).

Amylase is produced and released from a variety of tissues, including the salivary glands, intestine and genitourinary tract. Normal serum contains three types of isoamylases as identified by isoelectric focusing. The pancreatic gland secretes one amylase at an isoelectric point of 7.0 that constitutes 33% of the total normal serum amylase. The parotid secretes several isoamylases with iso- electric points of about 6.4 and 6.0. Electrophoresis on polyacrylamide gel can separate five isoamylases on the basis of electrode mobility. Amylases originating in the fallopian tubes, tears, mucus and sweat have the same mobility as salivary amylase. All amylases have similar molecular weight and amino acid composition, but vary in terms of their glycosylation or deamination.

Amylase is filtered through the glomerular membrane and is reabsorbed in the proximal tubule. In healthy individuals, the amylase clearance parallels creatinine clearance. During acute pancreatitis, there is an increase in amylase clearance as opposed to creatinine clearance. Although this ratio was once thought to be specific to acute pancreatitis, other conditions that produce hyperamylasemia (such as diabetic ketoacidosis, burns, renal failure and per—forated duodenal ulcer) may demonstrate a similar elevation. Occasionally, the serum amylase may be markedly increased in the absence of pancreatic or salivary diseases, whereas the urinary amylase is normal. In this instance, one must suspect either renal disease or macroamylasemia. In the latter condition normal serum amylase is bound by an immunoglobulin A (IgA), forming a complex that is too large to be filtered by the glomerulus. Affected individu—als have an elevated serum amylase and a low to normal urinary excretion rate.

Frequently physicians are faced with a patient who has no overt salivary gland disease but has hyperamylasemia and no specific abdominal findings. As a rule, the level of amylase in pancreatitis usually is elevated to greater than 3 times the upper limit of normal and returns to normal within 2 to 10 days. If the amylase continues to be elevated in the absence of pancreatic complications, other causes (such as malignancy and macroamylasemia) should be investigated.

A rapid rise and fall in serum amylase in a patient with abdominal pain suggests the passage of a stone through the ampulla of Vater. When the serum amylase remains elevated for several days, the gallstone disease is usually complicated by pancreatitis.

Marked hyperamylasemia has been observed in patients with metastatic disease with ovarian cysts and tumors, and in ruptured ectopic pregnancy. Isoamylase analysis reveals that the amylase has the same electrophoretic mobility as salivary-type isoenzyme. Macroamylase consists mostly of salivary amylase complexed with globulins, being therefore too large to be filtered at the glomerulus. Therefore these individuals have elevated serum amylase and low urinary amylase, with a low amylase-to-creatinine clearance ratio.

While the amylase levels in serum and urine are usually used as a measure of acute pancreatitis, measurements of lipase may be more specific and sensitive than total serum amylase. The assay of lipase is as accurate as the pancreatic isoamylase assay, and is likely to replace the amylase assay. Measuring both offers no advantage. Amylase and lipase measurements are readily available clinically, whereas radioimmunoassays are still being developed for other pancreatic enzymes (such as trypsin, chymotrypsin and elastase). Their role in the diagnosis of pancreatic disease needs to be established.

A recently developed urinary test for trypsinogen-2, which can be done with a urinary dipstick, appears to be quite promising in detecting patients with acute pan—creatitis. It has a sensitivity of 94% and a specificity of 95%, as compared to serum amylase assay which has a sensitivity of 85% and a specificity of 91%. A negative test rules out acute pancreatitis with a high probability. A positive result usually identifies patients in need of further evaluation.

4. Pancreatitis

4.1 Etiology and Pathogenesis

Inflammatory disease of the pancreas is a common problem in North America, with gallstones and alcohol being the major causes. Pancreatitis tends to present with abdominal pain, which may improve with no sequelae or may run a more severe course that can lead to death. When the pancreas is continuously injured, such as with alcohol, a chronic condition results in obstruction and fibrosis of the gland, which leads to pancreatic insufficiency and chronic pain. Even one attack of pancreatitis from alcohol use can lead to some residual pancreatic damage.

~~Pancreatitis results from an autodigestive process.~~ Inadvertent activation of trypsin and chemotrypsin in the pancreas is normally prevented by several protective mechanisms; these are overwhelmed in acute pancreatits, resulting in autodigestion. —Pancreatic digestive enzymes (including proelastase, procollagenase and phospholipases), vasoactive materials, and other toxic materials extravasate out of the pancreas into the surrounding areas, leading to a widespread chemical irritation ~~resulting in simple edema to severe hemorrhage and necrosis. Serious complications include hypovolemia and hypotension. Trypsin and chymotrypsin are the initiating enzymes; their release can in turn result in the release and activation of other proenzymes (including proelastase, procolla genase and phospholipases).~~ Trypsin damages endothelial cells and mast cells, resulting in the release of histamine. This major inflammatory mediator enhances vascular permeability, leading to edema, hemorrhage and the activation of the kallikrein system, which in turn results in the production of vasoactive peptides or kinins. The latter are thought to cause pain and further aggravate the inflammatory response. The other released enzymes destroy the supporting matrix of the gland and the plasma membrane of the acinar cell, precipitating further release of digestive enzymes, which in turn leads to further damage. Lysolecithin, which is released by the action of phospholipase on lecithin (a phospholipid found in bile), has also implicated in pancreatic damage, because of its cytotoxic and haemolytic properties.

Although the action of these enzymes results in pancreatic damage, the triggering mechanism is not well known. In the case of gallstone pancreatitis, major theories include (1) reflux of bile into the pancreatic duct (2) distal obstruction of the pancreatic duct by stones or oedema from recent stone passage. Here, continued pancreatic secretion results in increased ductal pressure.

When the pancreas is inflamed but remains viable, the condition is termed *interstitial pancreatitis*; this may occur in up to 80% of cases. In the remaining cases, there is a significant pancreatic necrosis resulting from disruption of the microcirculation, destruction of the pancreatic parenchyma and peripancreatic necrosis. This latter condition, necrotizing pancreatitis, follows a more protracted course. ~~Although the action of these enzymes results in pancreatic damage, the triggering mechanism is not well known. In the case of gallstones, the major theories include (1) reflux of bile into the pancreatic duct; and (3) distal obstruction of the~~

~~pancreatic duct, with continued pancreatic secretion leading to increased ductal pressure and resulting in pancreatitis.~~

Although alcohol has been implicated as a ~~major~~ cause of acute pancreatitis in at least 30% of cases, there is no evidence that an occasional bout of excessive alcohol intake can lead to an acute attack. It is suggested that chronic ingestion may lead to chronic damage and sensitization, which may lead to acute pain even with small amounts of alcohol. Alcohol can cause direct damage to acinar cells in a manner similar to that in which it damages liver cells.

Hyperlipoproteinemia types I1, 4 IV and V5 are associated with the majority of lipid-associated cases of pancreatitis. The incidence of pancreatitis vearies froorm 15-40% of patients. Hyperlipidemia has been suggested to be the cause of pancreatitis; however, recent evidence suggests that mild to moderate elevation of serum triglyceride levels is likely to be an epiphenomenon of the pancreatitis rather than the primary etiology. Hypercalcemia and hyperparathyroidism may also induce pancreatitis. Although the incidence of pancreatitis in patients with hyperparathyroidism was at one time shown to vary from 7-19%, recent findings suggest this variation to be closer to 1.5 % or less. This discrepancy can be accounted for by the difference in the degree or duration of the hyperparathyroidism and by the earlier treatment of hypercalcemia.

Other less common but important causes of acute pancreatitis include iatrogenic, through prescribed medications or following ERCP, ductal obstruction secondary to neoplasm, pancreas divisum, abdominal trauma, viral/parasitic infections, and hereditary causes. There is also a condition of Sphincter of Oddi dysfunction, which is associated with a higher risk of pancreatitis following ERCP.

4.2 Acute Pancreatitis

4.2.1 CLINICAL MANIFESTATIONS

The clinical spectrum of acute pancreatitis ranges from mild, self-limiting disease to fulminant lethal disease. Up to 80% of patients will have an uneventful recovery; the remainder will have serious complications with a high mortality rate. Objective measurements such as Ranson's criteria (Table 4) or APACHE II score, show a good correlation with the risk of major complications and death. Other methods of risk stratification have been developed for acute pancreatitis in the context of ERCP (Table 5). The overall mortality rate of acute pancreatitis ranges from 7–20%. The mortality rate correlates well with complications such as shock and hemorrhage.

Table 4. **Poor prognostic indicators in acute pancreatitis**

First 24 hours
Age >55
Leucocytosis >16,000
Hyperglycemia, serum glucose >11.1 mmol/L 200 mg/dL
LDH >350 units/L
AST>250 U/L

After 24 hours
Decrease in hematocrit by >10%
Hypocalcemia (<2.0 mmol/L)
Hypoxemia pO$_2$ <60 mmHg
Hypovolemia
Base deficit >4.0 meq/mmol/LAmylase >1,000

(Ranson's criteria, 1978, modified by Hollander et al., 1983)

Table 5. Risk factors associated with the development of post-ERCP pancreatitis

- Operator related
  - Lower ERCP volume

- Patient related
  - Suspected sphincter of Oddi dysfunction (SOD)
  - History of recurrent pancreatitis/post ERCP pancreatitis
  - Younger age
  - Normal bilirubin
  - Prior post-ERCP pancreatitis
  - Female sex (possible)

- ERCP method related
  - Difficult cannulation
  - Pancreatic duct injection
  - Pancreatic sphincterotomy
  - Precut sphincterotomy (by endoscopists of mixed experience)
  - Balloon dilation of biliary sphincter
  - Acinarization (possible)
  - Absent common bile duct stone (possible)

Abbreviation: CCK, cholecystokinin

Adapted from: Slivka A. *AGA Institute Postgraduate Course* 2006; page211-213.

4.2.2 SYMPTOMS

Pain from acute pancreatitis is a knife-like, steady, sharp pain that starts suddenly and reaches its zenith rapidly. It is commonly localized to the epigastric area and may radiate directly to the back. It improves on leaning forward and is frequently associated with nausea or vomiting. Depending on the location of the inflammation, the pain may be referred to either the left upper quadrant or the right upper quadrant. ~~When the pancreatitis is severe, it may result in shock and may lead to death.~~ Frequently the pain is dyspeptic in quality and aggravated by food. This is due partially to the fact that eating stimulates secretion. Classically the pain lasts between three and four days. When the pancreatitis is severe, it may result in peripheral circulatory failure; under these conditions, the mortality rate approaches 60%.

Recurrent nausea and vomiting may be due to a reflex mechanism secondary to pain and occurs in over 90% of the cases. Other causes include pseudo- obstruction secondary to ileus and distention or obstruction secondary to a pancreatic mass or pseudocyst. Since the common bile duct traverses the pancreatic head before entering the duodenum, jaundice may occur, often transiently.

4.2.3 SIGNS

Depending on the severity of pancreatitis, the patient may appear in distress or be in shock. Jaundice may be caused by edema of the head of the pancreas or by an obstructing stone. Tachycardia could be secondary to pain, volume depletion or the inflammatory process. Low-grade fever could be secondary to the inflammation in the pancreas or result from such

complications as abscess formation.

Abdominal examination may reveal epigastric and abdominal tenderness with guarding or rigidity. Bluish discoloration of the flanks (Grey Turner's sign) or of the periumbilical area (Cullen's sign) indicates that blood from hemorrhagic pancreatitis has entered the fascial planes. The signs are not specific and may occur in any condition that causes retroperitoneal hemorrhage. Tender red and painful nodules that mimic erythema nodosum may appear over the extremities. These are often due to circulating lipases.

The investigation of the structural disorders of the pancreas by ERCP is slowly being replaced by MRI imaging (MRCP). This is because ERCP may be associated with the development of mild to moderately severe pancreatitis (Table 5). If MRCP shows an abnormality in the pancreas that needs to be treated by ERCP (rather than just investigation), then the risk of the development of ERCP-associated pancreatitis needs to be accepted.

4.2.4 COMPLICATIONS

Since the signs and symptoms of acute pancreatitis may mimic those of surgically correctable intra-abdominal disorders, the diagnosis of acute pancreatitis is often one of exclusion. Other diseases to be considered are a perforated peptic ulcer, mesenteric thrombosis, intestinal obstruction, dissecting aneurysm, peritonitis, acute cholecystitis and appendicitis. The diagnostic process is complicated by the fact that hyperamylasemia can occur in disorders other than pancreatic inflammation (such as ectopic pregnancy, parotiditis, carcinoma of the lung, posterior penetrating ulcer, ruptured aortic aneurysm and opiate administration). Although amylase values greater than 1,000 units have been said to occur principally in conditions requiring surgery (e.g., biliary tract disease), this distinction is not absolute.

Local involvement of pancreatitis includes phlegmon (18%), pancreatic pseudocyst (10%), pancreatic abscess (3%) and thrombosis of the central portal system. Phlegmon is an area of edema, inflammation and necrosis without a definite structure (unlike an abscess). A phlegmon results from acute intrapancreatic inflammation with fat necrosis and pancreatic parenchymal and peri- pancreatic necrosis. This arises from the ischemic insult caused by decreased tissue perfusion and release of the digestive enzymes. When this damage is not cleared, further inflammation ensues, declaring itself by increased pain, fever and tenderness. In severe cases a secondary infection ensues, a process termed *infected necrosis of the pancreas*, which occurs within the first one to two weeks of the illness and carries a high mortality. This diagnosis can be made by CT and percutaneous aspiration of the area with subsequent bacterial staining and appropriate cultures. In 3% of acute pancreatitis cases an abscess develops, usually several weeks into the illness. An abscess is a well-defined collection of pus occurring after the acute inflammation has subsided.

A pseudocyst develops as a result of pancreatic necrosis and the escape of activated pancreatic secretions through pancreatic ducts. It contains blood and debris. This fluid coalesces and becomes encapsulated by an inflammatory reaction and fibrosis. These patients usually have pain and hyperamylasemia, but may be asymptomatic. They may present with an abdominal mass, causing compressive symptoms.

Systemic complications of acute pancreatitis are numerous (Table 6) and correlate well with the severity of the inflammatory process. They may be manifested by shock (circulatory collapse secondary to sequestration of retroperitoneal fluid or hemorrhage), respiratory and renal failure and profound metabolic disturbances.

Table 6. **Complications of pancreatitis**
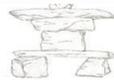
- Local
  - Sterile necrosis
  - Infected necrosis
  - Abscess
  - Pseudocyst
  - Gastrointestinal bleeding

- Pancreatitis-related:
  - Splenic artery rupture or splenic artery pseudoaneurysm rupture
  - Splenic vein rupture
  - Portal vein rupture
  - Splenic/portal vein thrombosis, leading to gastroesophageal varices with rupture
  - Pseudocyst or abscess hemorrhage
  - Postnecrosectomy bleeding
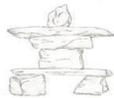
- Non-pancreatitis-related:
  - Mallory-Weiss tear
  - Alcoholic gastropathy
  - Stress-related mucosal gastropathy

- Splenic injury
  - Infarction
  - Rupture
  - Hematoma

- Fistulization to or obstruction of small or large bowel

- Right-sided hydronephrosis

- Systemic (systemic cytokine response, aka "cytokine" storm)
  - Respiratory failure
  - Renal failure
  - Shock (circulatory failure)
  - Hyperglycemia
  - Hypoglycemia
  - Hypocalcemia
  - Hypomagnesemia
  - Disseminated intravascular coagulation
  - Subcutaneous nodules due to fat necrosis
  - Retinopathy
  - Psychosis
  - Malnutrition
  - Death

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): page 524.

Although acute pancreatitis may run a mild self-limiting course, severe pancreatitis occurs in up to 25% of acute attacks, with a mortality approaching 10%. The majority of deaths occur within the first week of hospital admission and are caused by local and systemic complications, including sepsis and respiratory failure. Most clinical studies in the adults cite pancreatic infection as the most common cause of death, accounting for 70–80% of deaths.

4.2.5 DIAGNOSTIC EVALUATION

Since the signs and symptoms of acute pancreatitis may mimic those of surgically correctable intra-abdominal disorders, knowledge and consideration of the differential diagnosis for acute pancreatitis is an important part of the initial evaluation. This includes: perforated peptic ulcer, mesenteric ischemia/infarction, intestinal obstruction, dissecting aneurysm, peritonitis, acute cholecystitis, biliary colic, inferior wall myocardial infarction, ectopic pregnancy, and appendicitis. The diagnostic process is complicated by the fact that

hyperamylasemia can occur in disorders other than pancreatic inflammation (such as ectopic pregnancy, parotiditis, carcinoma of the lung, posterior penetrating ulcer, ruptured aortic aneurysm and opiate administration: see table 2). Although amylase values greater than 1,000 units have been said to occur principally in conditions requiring surgery (e.g., biliary tract disease), this distinction is not absolute.

The diagnosis of acute pancreatitis is based on consideration of the above mentioned symptoms and signs,a combination of clinical find ings and the use of laboratory and radiographic techniques. Elevation of serum amylase in acute pancreatitis is short-lived. Amylase is rapidly cleared by the renal tubules and although it can stay elevated for several days, it may return to normal within 24 hours from the time of onset. Although amylase to creatinine clearance was used in the past to diagnose pancreatitis, it is now rarely used. Lipase levels appear to be a more sensitive and specific method of diagnosing acute pancreatitis and may remain elevated forlonger than serum amylase several days following the onset of pain. Immunologic assays for trypsinogen or immunolipase are experimental and do not add any more information than the serum lipase.

Although not diagnostic, it is important to complete lab workup of a patient with pancreatitis. A CBC should be ordered, as white blood count may be elevated in these patients, hemorrhagic pancreatitis may occour, and a high MCV may point to alcohol as a cause of pancreatitis. Liver enzymes may also be elevated; particularly in the setting of gallstone pancreatitis.

4.2.6 RADIOLOGIC EVALUATION

A plain film of the abdomen is very helpful. It may reveal calcification of the pancreas (indicative of a chronic process) or it may reveal gallstones (if calcified). The presence of free air suggests perforation, whereas the presence of thumb-printing in the intestinal wall may indicate a mesenteric ischemic process. A localizing ileus of the stomach, duodenum or proximal jejunum (all of which are adjacent to the pancreas) is highly suggestive of pancreatic inflammation. Similarly, when the transverse colon is also involved, air filling the transverse colon but not the descending colon (colon "cut-off" sign) may be seen. The chest x-ray can show atelectasis or an effusion, more often involving the left lower lobe.

Although clinical, biochemical and simple radiographic evaluation suffice for the diagnosis of pancreatitis, ultrasonographic and computerized tomography imaging are essential. Additional imaging such as MRCP, ERCP, or EUS, may also be indicated These tests provide clues as to etiologyconfirm the diagnosis, detect the presence/location of stones, help delineate relevant anatomy, provide an early assessment regarding the course of the diseaseseverity, and detect complications such as phlegmon, pseudocyst and abscess formation. A pseudocyst or an abscess may also be drained percutaneously under CT or ultrasound guidance. There are numerous tests for the detection of large and multi ductal diseases in persons with chronic pancreatitis (Table 7).

➢ The most common ultrasonographic and CT finding in patients with acute pancreatitis is diffuse glandular enlargement. Ultrasonographically there is a decrease in echogenicity of the organ; on CT scan there is decreased attenuation from edema of the tissues. Frequently intravenous contrast is given, and this may demonstrate a uniform enhancement in the pancreatic parenchyma. Contrast enhanced CT useful to grade pancreatitis, and to detect necrosis as well as neoplasm. In this regard, it is equivalent to gadolinium-enhanced

dynamic MRCP. However, both contrast-enhanced MRCP and EUS are superior to contrast enhanced CT to detect CBD stones. (Arvanitakis M, et al. *Gastroenterology* 2005:715-23.

➤ A normal <u>CT</u> examination does not rule out the presence of acute disease. In up to 30% of uncomplicated cases of acute pancreatitis CT scan may be normal; these patients usually have a mild form of pancreatitis. <u>(ie: grade "A", see below)</u> When a stone or an obstruction of the distal common bile duct is present, ~~the common bile duct and the intrahepatic biliary tree may be dilated~~<u>CT may demonstrate dilatation of the common bile duct, or of the intrahepatic biliary tree. Ultrasound is able to diagnosis dilated common bile duct 55-91% of the time, and is able to pick up common bile duct stones 20-75% of the time. This is in contract to detection rate of gallstones, where the accuracy of ultrasound in detection is greater than 90%. Ultrasound is, however, not useful to ascertain severity of pancreatitis.</u>

○ <u>This is best done with CT or MRI.</u>
➤ <u>Accepted criteria for grading severity of pancreatitis on CT have been established. These criteria, termed the "Balthazar severity index" use a grading scale of A to E, where grade A is normal appearing pancreas, grade C involves peripancreatic inflammation, and grades D and E involve peripancreatic fluid collection or several collections/evidence of pancreatic or retroperitoneal gas.</u>

ERCP <u>is an invasive diagnostic and therapeutic procedure that</u> involves the cannulation of the ampulla of Vater and then injection of contrast material into the pancreatic duct and the biliary tree. This procedure is usually contraindicated during the acute phase, except when the pancreatitis is caused by an impacted common bile duct stone. Under those conditions, a sphincterotomy and stone removal may be performed. If performed as early as 24 hours following admission, this procedure may result in significant improvement in morbidity and mortality.

Table 7. Tests use for the detection of large and small duct disease in persons with chronic pancreatitis

Diagnostic test	Possible findings in 'big duct' disease	Findings in 'small duct' disease
➤ Fecal elastase	○ Usually low (<100/g of stool)	○ Usually normal
➤ Serum trypsin	○ Usually low (<20 ng/mL)	○ Usually normal
➤ Abdominal ultrasonography	○ Pancreatic atrophy, pancreatic duct dilation, pancreatic calcifications, pseudocyst	○ Usually normal
➤ Computerized tomography	○ Pancreatic atrophy, pancreatic duct dilation, pancreatic calcifications, pseudocyst	○ Usually normal or equivocal
➤ MRCP	○ Pancreatic atrophy, pancreatic duct dilation, irregularity or stricture, pancreatic calcifications, pseudocyst	○ Usually normal or equivocal

Diagnostic test	Possible findings in 'big duct' disease	Findings in 'small duct' disease
➢ Endoscopic ultrasonography	o Abnormal (>4 features of chronic pancreatitis)	o May be abnormal
➢ ERCP	o Abnormal	o Normal or minimally abnormal
➢ Direct hormonal stimulations test (e.g. secretin test)	o Abnormal	o Usually abnormal

Abbreviations: MRI, magnetic resonance imaging, MRCP, magnetic resonance cholangiopancreatography.

Printed with permission: Lieb JG II, and Forsmark CE. Review article: Pain and Chronic Pancreatitis. *Aliment Pharmacol Ther.* 2009;29(7):706-19.

4.2.7 TREATMENT

The aims of therapy of acute pancreatitis are (1) hemodynamic stabilization, (2) alleviation of pain, (3) stopping the progression of the damage, and (4) treatment of local and systemic complications. As yet there are no specific medical therapies capable of reducing or reversing the pancreatic inflammation. Hence therapeutic interventions are aimed at the complications of the disease.

Once the diagnosis is established with certainty, the patient's intravascular volume is replenished, and electrolytes, calcium, magnesium and blood sugar are closely monitored. Depending on the severity of the attack, an indwelling urinary catheter and close monitoring of urinary output may be necessary. Analgesics such as meperidine should be administered regularly during the first several days of the attack. This may alleviate the pain, decrease the patient's apprehension and improve respiration, thus preventing pulmonary complications such as atelectasis. The risk of narcotic addiction is minimal during the first days; most patients settle within 72 hours. The patient is kept off oral feeding; nasogastric suctioning is maintained only if if the disease is severe and complicated by intractable vomiting and ileus. Mild cases with minimal symptoms may be managed without suctioning. The rationale behind nasogastric suctioning is to place the pancreas at rest by removing the acidic gastric juices. This suppresses secretin release and decreases pancreatic stimulation. The validity of this postulate has not been substantiated. Similarly, the use of acid-suppressive medications such as cimetidine has failed to show benefit in the treatment of acute pancreatitis. The use of enzyme inhibitors such as soy-bean trypsin inhibitor to prevent further damage is controversial, as is the use of prostaglandins and corticosteroids.

The routine administration of antibiotics does not improve the course of mild to moderate disease. However, when the development of pancreatic abscess is suspected from an increase in fever and abdominal pain, antibiotic therapy should be instituted. The use of prophylactic antibiotics in the setting of necrotizing pancreatitis is controversial.

Respiratory insufficiency may occur in up to 40% of the cases, usually in patients with severe or recurrent pancreatitis. In such patients, arterial oxygen saturation should be monitored and corrected. Fluid overload should be avoided. Intubation and ventilation may be required.

Peritoneal lavage has been advocated in patients with severe disease, such as those with marked hypovolemia or hypotension or those who continue to deteriorate despite appropriate medical therapy. Although this technique reduces the circulatory and renal complications, it does not seem to alter the local complications.

Intravenous hyperalimentation has been advocated in patients who contin-ue to have pain and whose symptoms are aggravated postprandially. Several studies have documented equally effective results with nasoenteric alimentation.

If during a trial of six weeks or longer, complications develop (such as an abscess or an enlargement of phlegmon), a surgical debridement may be warranted, albeit as a last resort. Several studies have documented equally effective results with enteral alimentation.

4.3 Chronic Pancreatitis

Chronic pancreatitis is defined as a continued inflammation characterized by irreversible morphologic changes. These changes include fibrosis, ductal abnormality, calcification and cellular atrophy. Alcohol is the major etiologic factor, accounting for about 75% of the cases. Repeated attacks of gallstone- related pancreatitis rarely if ever result in chronic pancreatitis. Other causes include diabetes, protein-calorie malnutrition, hereditary pancreatitis, cystic fibrosis, hypertryglyceridemia, hypercalcemia, tropical pancreatitis, autoimmune pancreatitis, and idiopathic causes.

Recent evidence suggests the possibility that some patients with chronic pancreatitis have a mutation of the CFTR or SPINK 1 gene (see Section 8) that predisposes them to this complication. This may explain These cases may explain some of the cases of idiopathic or familial pancreatitis.

Alcohol presumably causes pancreatic injury by the intraductal formation of protein plugs secondary to increased protein concentration and precipitation, with or without calcification. These plugs lead to obstruction and secondary pancreatic damage caused by autodigestion. In developed countries chronic pancreatitis occurs after a long history (6 to 17 years) of alcohol ingestion of 150 to 170 g per day. Alcoholic pancreatitis is known to occur with much less consumption of alcohol, as low as 50 g per day. The mean age of a patient with new onset of disease is around 32 years, with a male predominance. Despite heavy drinking only a small number opercentage of alcoholics develop chronic pancreatitis, suggesting other factors that potentiate the injurious side effects of alcohol, including. Potential cofactors include smoking (very high association with alcohol pancreatitis and may be independent risk factor)itis, high-protein diet with either very high or very low fat content, genetic mutations, and type of alcohol/manner of ingestion.

Table 8: Causes of Chronic Pancreatitis

➢ Duct obstruction
- o Benign pancreatic duct obstruction
    - Traumatic stricture
    - Stricture after severe acute pancreatitis
    - Duodenal wall cyst
    - Pancreas divisum

Formatted: Indent: First line: 0", Line spacing: single

Formatted: Bullets and Numbering

‒ Sphincter of Oddi Dysfunction (SOD)

- o Malignant pancreatic duct stricture
  - – Ampullary or duodenal carcinoma
  - – Pancreatic adenocarcinoma
  - – Intraductal papillary mucinous neoplasm

- ➤ Hereditary
  - o CT (cationic trypsinogen) gene
  - o Autosomal dominant
    - – Hereditary pancreatitis (PRSS1 mutations)
  - o Autosomal recessive or modifier genes
    - – CFTR mutations
    - – SPINK1 mutations
    - – IgG4 associated

- ➤ Autoimmune
  - o Associated with autoimmune diseases (eg. Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis)

- ➤ Tropical
  - o Tropical calcific pancreatitis
  - o Fibrocalculous pancreatic diabetes

- ➤ Metabolic
  - o Diabetes
  - o Alcohol
  - o Hypercalcemia
  - o Hyperlipidemia
  - o Hypertriglyceridemia
  - o Lipoprotein lipase deficiency
  - o Apolipoprotein C-II deficiency

- ➤ Postnecrotic chronic pancreatitis

- ➤ Idiopathic
  - o Early-onset
  - o Late-onset

- ➤ Asymptomatic pancreatic fibrosis
  - o Chronic alcoholism
  - o Old age
  - o Chronic renal failure
  - o Radiotherapy

Adapted from: Chari ST. *Mayo Clinic Gastroenterology and Hepatology Board Review*; pg 470.; Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 1274.; and 2010, page 988; and Keller J, and Layer P. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): page 106.

4.3.1 CLINICAL MANIFESTATIONS

Chronic pancreatitis is characterized by irreversible injury to the pancreas and clinically by intractable abdominal pain and loss of exocrine and endocrine pancreatic function. The pain is localized to the upper abdomen, with radiation to subcostal regions and to the back. The pain is aggravated by meals and improves with fasting.

When more than 90% of exocrine pancreatic function is lost, maldigestion and malabsorption ensue. This is manifested by steatorrhea (fat malabsorption) associated with diarrhea and bloating, azotorrhea (protein malabsorption) and progressive weight loss. These patients frequently present with loss of adipose tissue, judged by hanging skin folds, and more objectively by demonstrating that the skin fold at the mid triceps is less then 8 mm in males and less than 12 mm in females. In addition, they manifest muscle wasting and edema, indicating protein deficiency. Latent fat-soluble vitamin deficiency (vitamins A, D, E and K) in addition to deficiencies of magnesium, calcium and essential fatty acids may occur and are closely related to dysfunction of fat digestion. Endocrine insufficiency presenting as diabetes mellitus may present at the same time as exocrine insufficiency or years a few years later.

One exceptional presentation is that of autoimmune pancreatitis, which, although a cause of chronic pancreatitis, can initially present as painless jaundice mimicking pancreatic cancer. In this setting, both diagnoses must be carefully considered. (see table 9).

4.3.2 COMPLICATIONS

Numerous tests are available to detect ductular disease in persons with chronic pancreatitis (Table 7).

4.3.2.1 Pancreatic pseudocyst

Pancreatic pseudocyst is localized fluid collection occurring within a pancreatic mass or in the peripancreatic spaces following acute or chronic pancreatitis (Figure 5). The pseudocyst is usually surrounded by a non-epithelial-lined fibrous wall of granulation tissues. Its frequency varies from 10–50% of patients experiencing severe pancreatitis. When a pseudocyst is present for less than six weeks, it is considered acute; after that it becomes chronic. The pseudocyst may be asymptomatic or may present as an acute exacerbation of pancreatitis, with abdominal pain, nausea, vomiting and weight loss. These pseudocysts may obstruct intra-abdominal viscera, cause pancreatic ascites, rupture into viscera or the abdominal cavity, hemorrhage or become infected. Spontaneous resolution occurs in 20% of the cases within the first six weeks of the pseudocyst's development. Chronic pseudocysts or pseudocysts greater than 5 cm rarely improve. Asymptomatic patients with persistent pseudocysts should be observed and intervention may be considered if symptoms appear. Successful percutaneous catheter drainage may be accomplished by CT- or ultrasound- guided drainage techniques. The catheter may be required for up to six weeks and is frequently associated with infections. Surgical drainage is sometimes necessary for failed percutaneous drainage or for complicated pseudocysts. If the pseudocyst is in the head of the pancreas, drainage can be done via ERCP.

4.3.2.2 Pancreatic ascites

Pancreatic ascites results from the leakage of pancreatic juices into the peritoneal cavity through a fistula or a ruptured pseudocyst. It presents with gradually increasing massive ascites, with high levels of amylase, abdominal pain and weight loss. Painful areas of subcutaneous fat necrosis result from the high levels of circulating pancreatic lipase.

Figure 5. Pancreatic foil pseudocyst. Transverse sonogram showing a cystic septated well-defined mass in the pancreatic tail. It is touching and compressing the line of the splenic vein.

4.3.2.3 Common bile duct stricture

Common bile duct compression is another manifestation of chronic pancreatitis, but it rarely results in significant obstruction. As the distal common bile duct traverses the head of the pancreas, it may be narrowed secondary to inflammation, with edema or fibrosis of the gland.

PAlthough pancreatic carcinoma, a cause of common bile duct stricture, was formerly thought to be increased in chronic pancreatitis. T, the incidence is now believed to be the same as in the general population. Importantly however, pPancreatic carcinoma may present as pancreatitis.

4.3.2.4 Other complications

Gastric outlet obstruction can result during an acute flare. Similarly, inflammation can result in splenic vein thrombosis, which in extreme cases can lead to left sided portal hypertension and gastric variceal bleeding.
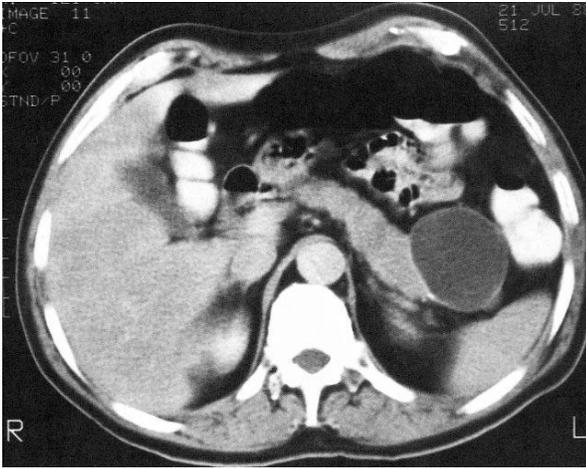
Figure 6. Computerized tomography of a pancreatic pseudocyst in the tail of the pancreas.

4.3.3 DIAGNOSTIC AND RADIOGRAPHIC EVALUATION

Causes of chronic pancreatitis.

➤ Duct obstruction
  o Benign pancreatic duct obstruction
    - Traumatic stricture
    - Stricture after severe acute pancreatitis
    - Duodenal wall cyst
    - Pancreas divisum
  o Malignant pancreatic duct stricture
    - Ampullary or duodenal carcinoma
    - Pancreatic adenocarcinoma
    - Intraductal papillary mucinous neoplasm

➤ Hereditary
  o CT (cationic trypsinogen) gene
  o Autosomal dominant
    - Hereditary pancreatitis (PRSS1 mutations)
  o Autosomal recessive or modifier genes
    - CFTR mutations
    - SPINK1 mutations
    - IgG4 associated

➤ Autoimmune
  o Associated with autoimmune diseases (eg. Sjögren's syndrome, primary biliary cirrhosis, primary sclerosing cholangitis)

➤ Tropical
  o Tropical calcific pancreatitis
  o Fibrocalculous pancreatic diabetes
➤ Metabolic
  o Diabetes
  o Alcohol
  o Hypercalcemia
  o Hyperlipidemia
  o Hypertriglyceridemia
  o Lipoprotein lipase deficiency
  o Apolipoprotein C-II deficiency

➤ Postnecrotic chronic pancreatitis

➤ Idiopathic
  o Early-onset
  o Late-onset

First Principles of Gastroenterology and Hepatology   A. B. R. Thomson and E. A. Shaffer

➢ ~~Asymptomatic pancreatic fibrosis~~
  - ~~Chronic alcoholism~~
  - ~~Old age~~
  - ~~Chronic renal failure~~
  - ~~Radiotherapy~~

~~Adapted from: Chari ST.~~ *~~Mayo Clinic Gastroenterology and Hepatology Board Review~~*~~; pg 470.; Forsmark CE.~~ *~~Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management~~* ~~2006: pg. 1274.; and 2010, pg. 988; and Keller J, and Layer P.~~ *~~Best Practice & Research Clinical Gastroenterology~~* ~~2008; 22(1): pg. 106.~~

The diagnosis of chronic pancreatitis is straightforward in patients with advanced pancreatic disease. This can be demonstrated by the presence of calcification seen exclusively in the ductal system on plain radiographic abdominal films, by ultrasonography or on computerized tomography. ~~The r~~However, radiologic evidence ~~may be seen~~is only seen in up to 30% of patients with chronic pancreatitis.

Although ultrasonography may demonstrate pancreatic enlargement, ductal dilatation or pseudocysts, these findings ~~may be~~are better seen on computerized tomography (Figure 6).

The role of Endoscopic ultrasound (EUS) in evaluation of chronic pancreatitis is evolving. The advantage of EUS, is the ability to provide information about the pancreatic parenchyma, as well as the ducts. Problems of interpretation may arise in these patients, particularly in older adults or alcoholics whose senile or fibrotic changes may be misinterpreted as a reflection of underlying chronic pancreatitis.

MRCP can provide detailed information about the pancreas and surrounding tissues. Large dilated ducts, as well as structural abnormalities, can be detected. However, small duct changes and calcifications are not well visualized.

ERCP is quite sensitive and specific for diagnosis of moderate to severe pancreatitis. In more severe disease there is narrowing and dilation of the ducts, stenosis, and filling of side ductules~~Abnormalities of the ducts associated with chronic pancreatitis can also be demonstrated by ERCP. In mild to moderate disease these findings may be subtle and even normal.In more severe disease there is narrowing and dilation of the ducts, stenosis and filling of side ductules~~ Examination may reveal a tortuous main duct containing stones or protein plugs, or obstruction of the common bile duct (Figure 7). In mild to moderate disease, however, ERCP findings may be subtle and even normal. Also, ERCP~~These~~ changes may not be closely related to the degree of pancreatic insufficiency; hence the ~~need~~rationale for pancreatic function studies in evaluating chronic pancreatitis.~~.~~

The only pancreatic function ~~tests~~ that appear to accurately measure pancreatic function in chronic pancreatitis are the direct tube tests that measure the response of the pancreas to various stimuli. The commonest manifestation is a decreased bicarbonate concentration (< 50 mEq/L) and decreased volume of secretion.

When no cause of the pancreatitis is found, the condition is considered to be "idiopathic". Microlithiasis (stones <3mm) occur in 37-89% of persons with idiopathic acute pancreatitis, and some experts recommend cholecystectomy for associated symptoms. Biliary crystals, crystals of calcium bilirubinate, calcium carbonate, or cholesterol monohydrate, can contribute. The use of duodenal drainage to assess the presence of biliary crystals has a sensitivity of 65%, and a specificity of 94-100%

HoweverOverall, extensive investigation of the patient is necessary before that the diagnosis of idiopathic chronic pancreatitis is made (Table 8).
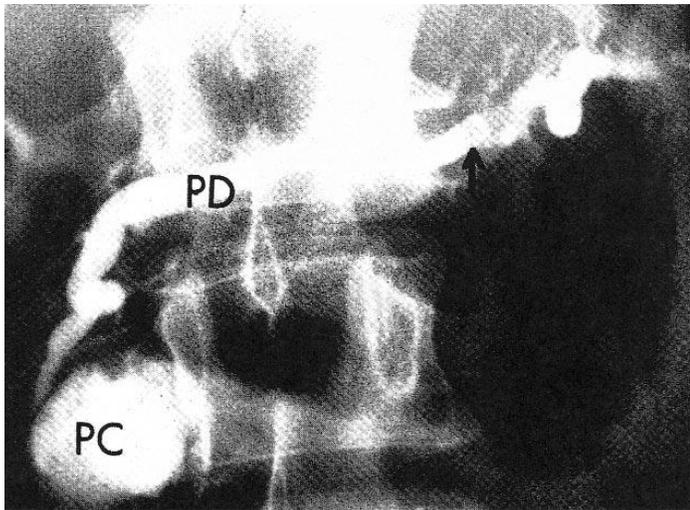
Figure 7. ERCP of a patient with a chronic pancreatitis demonstrating dilation of the duct (PD) with filling of side branches in the tail. This is complicated by pancreatic pseudocyst (PC).

Table 8. ~~Tests to do to seek a cause of pancreatitis prior to diagnosing the patient as having idiopathic pancreatitis~~ **Workup: Chronic Pancreatitis**

➢ Structural (ERCP/MRCP, CT)
   o Pancreas Divisum, chronic pancreatitis, ampullary stenosis, juxta-ampullary diverticulum, or other anatomic abnormalities.
   o ERCP with bile aspiration, centrifugation and examination of pellet for biliary crystals
   o SOD (Sphincter of Oddi) dysfunction (pressure measurement)

➢ Hereditary
   o CFTR gene
   o cationic trypsinogen (CT) gene
   o SPINK gene
   o Tests for autoimmune pancreatitis: (for details, see Table 9)

 (IgG4 level); Sphincter of Oddi pressure measurement for SOD (sphincter of Oddi dysfunction)

There are strict criteria that must be met before the diagnosis of autoimmune pancreatitis is made, and the patient is treated with glucocorticosteroids ("steroids") (Table 9).

Table 9. **Criteria for the diagnosis of autoimmune pancreatitis (AIP), and the features characteristic for the diagnostic groups**

- ➤ Diagnostic criteria
  - o Clinical
    - More frequently males (80%), over 50 years (80%)
    - Pain is not a prominent feature

- o Histology
  - Periductal lymphoplasmacytic infiltrate with obliterative phlebitis (LPSP) in pancreatic tissue
  - High (>10 cells/hpf) igG4 positive cells in the pancreas
  - Lymphoplasmacytic infiltrate with fibrosis in the pancreas
- Imaging
- o Type I, lymphoplasmacytic sclerosing pancreatitis, and type II idiopathic duct centric pancreatitis
  - Typical: diffusely enlarged gland with delayed 'rim' enhancement, diffusely irregular, attenuated main pancreatic duct
  - CT/MRI shows "sausage-shaped" enlargement of pancreas, peripheral (RIM) enhancement, and delayed enhancement; ERCP shows characteristic diffusely irregular and narrowed pancreatic duct.
  - Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis
  - Focal, but usually diffuse involvement of pancreas with irregular narrowing of pancreatic duct, swelling of parenchyma, from periductive lymphoplasmacytic, infiltration, storiform fibrosis, obliterative phlebitis (infiltrative surrounds venules but not arteriols), and IgG4 positive immunostaining of $\geq$ IgG4 positice cells per HPF
- o Serology
  - Elevated serum IgG4 level (normal 8-140 mg/dl)
  - Elevated serum IgG4 is 75% sensitive and 93% specific for AIP; IgG4 > 2XULN are highly specific, but ↑ IgG4 may also be seen in 1.5% of pancreatic cancers
- IgG4-associated systemic disease (ISD) (Chari 09)
- o Other organ involvement
  - ISD may affect pancreas, bile ducts, salivary glands, kidneys, retroperitoneum, and lymph nodes
  - Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
- o Response to steroid therapy
  - Resolution or marked improvement of pancreatic /extrapancreatic manifestation with corticosteroid therapy
  - Consistent response to 30-40 mg prednisone, tapering with improvement in serum IgG4 and imaging

Abbreviations: HPF, high power field; IgG4, immunoglobulin G4; AIP, autoimmuine pancreatitis; ISD, IgG4-associated systemic disease

Printed with permission: Dite, Petr., et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): page 138.

4.3.4 ~~TREATMENT~~MANAGEMENT

The ultimate goals of treatment in chronic pancreatitis are to alleviate pain, maintain adequate nutritional status, and reduce symptoms associated with steatorrhea such as abdominal pain, bloating and diarrhea.

The mechanism of pain in chronic pancreatitis is not known. There are numerous approaches to the management of pain in chronic pancreatitis which need to be carefully considered (Table 10). Endoscopic procedures play an important role in the management of patients with acute or chronic pancreatitis (Table 11). Despite the many positive uses of endoscopic management, there are clear indications for surgery (Table 12).

Table 10. Approaches to the management of pain in the patient with chronic pancreatitis

- General measures
  - 1. Manage associated/causative factors

  - 2. Cessation smoking and ~~of~~ alcohol intake
  - 3. Analgesics
  - 4. ~~Gabbapentum~~Gabapentin,
  - SSRIs, TCAs
  - 5. Low-fat diet

- Neural interruption
  - Percutaneous or endoscopic (EUS) nerve blocks (data promising)
  - Surgical (thorascopic) splanchnic nerve resection

- Reduction of intrapancreatic pressure
  - Suppression of enzyme secretion
  - Anticholinergics, PPI, somatostatin, pancreatic enzyme replacement
  - Decompression techniques
    - Sphincterotomy, endoscopic dilation and stenting
    - Stone removal (endoscopic or ESWL)
  - Surgical drainage, if pancreatic duct dilated ~~(Peustow)~~
  - Organ resection
    - Partial for persistent inflammatory mass, complete for refractory cases, with/without pancreatic islet cell transplant

Adapted from: Forsmark CE. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg 1288-1294.

Some of the methods found to help relieve the pain from chronic pancreatitis involve endoscopic procedures (Table 11) or the use of nasogastric drainage of the duodenal lumen.

Table 11. **Roles of endoscopic procedures in the management of acute/chronic pancreatitis**

- ERCP
  - Sphincterotomy
  - Dilation and stenting of pancreatic strictures
  - Removal of pancreatic duct stones
  - Pancreatic duct disruption and pseudocyst
  - Biliary strictures from chronic pancreatitis
  - Pancreas divisum
  - Aspirate cyst fluid

- EGD
  - Jejunal tube placement for enteral feeding

- EUS

- o   Diagnosis of CBD stones
- o   Celiac nerve block and neurolysis

Table 12. **Indications for surgery in persons with chronic pancreatitis**

- Intractable pain
- Suspicion of malignancy
- Common bile duct obstruction
- Symptomatic duodenal obstruction
- Symptomatic pseudocysts[a]
- Vascular obstruction[b]
- Pancreatic duct obstruction[b]

[a]Both surgical and endoscopic drainage procedures are possible
[b]If present with other complications

Printed with permission: Mihaljevic AL, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): page 170.

Abstinence from alcohol may decrease the frequency and severity of painful attacks in patients with alcoholic pancreatitis. Large meals with foods rich in fat should be avoided. Analgesics should be given prior to meals, since the pain is maximal postprandially. The continuous use of narcotics often leads to drug addiction, which makes the management of pain more difficult. Large doses of pancreatic extracts may reduce the frequency and severity of the pain in patients with no demonstrable duct obstruction. These enzymes appear to suppress pancreatic exocrine output, thus putting the pancreas at rest and resulting in pain relief. Pancreatic replacement is given with meals and at bed—time. Patients who respond to this therapeutic regimen tend to be middle-aged women with idiopathic pancreatitis who suffer from mild or moderate disease. These patients tend to have a bicarbonate output greater than 55 mEq/L and normal fat absorption. Patients with more severe disease, whose peak bicarbonate output is less than 50 mEq/L, tend not to respond to this regimen.

Patients with intractable pain who fail to respond to medical therapy may benefit from surgical intervention. When there is a dilated pancreatic duct with obstructive areas, longitudinal pancreatojejunostomy (modified Pustow operation) may induce immediate pain relief. When the duct is small, partial surgical resection of the pancreas may control the pain in a certain percentage of patients. Although pain alleviation with surgery may be achieved in certain patients, its long-term benefit is limited since pain recurs in the majority of patients. An alternative to surgical drainage may be achieved by endoscopic insertion of an endoprosthesis (stent) into the pancreatic duct. Although this approach is promising, its long-term benefit has not been proven.

Octreotide, a long-acting somatostatin analogue, appears to decrease the pain of chronic pancreatitis. Its action is mediated by suppressing pancreatic secretion, hence resting the pancreas. The role of octreotide remains uncertain.

Administration of high-potency, enteric-coated pancreatic enzymes remains the main therapy for the treatment of steatorrhea in the majority of patients with idiopathic and

alcoholic pancreatitis. This will improve fat digestion, increase absorption and allow weight gain, although it will not correct the steatorrhea completely. Azotorrhea is more easily reversed than steatorrhea, since trypsin is more resistant to acid inactivation than lipases. It seems that the most important barrier preventing correction of steatorrhea is the destruction of enzymes in the stomach, which prevents the delivery of enough active enzyme into the duodenum.

Replacement pancreatic enzymes are made from hog pancreas and contain a mixture of proteases, lipase and amylase, along with a variety of enzymes normally present in pancreatic secretions. Different preparations vary in the amount of lipase activity and the method of enzyme delivery (e.g., tablets, capsules or enteric-coated microspheres). Treatment with these enzymes is lifelong. Pancreatic enzymes are inactivated by pH 4 or below; hence, enteric- coated preparations such as Pancrease® or Cotazym® may be appropriate. In patients who do not respond well, the use of ~~histamine H$_2$ receptor antago nists (cimetidine, ranitidine or famotidine)~~ proton pump inhibitors or antacids with meals may over—come the detrimental effect of acid on the enzymes. The causes of failure to respond to pancreatic enzyme supplementation are shown in Table 13.

Table 13. **Causes of failure of pancreatic replacement**

- o Incorrect diagnosis (nonpancreatic causes of steatorrhea, such as sprue, bacterial overgrowth)
- o Poor compliance
- o Incorrect timing of the medication (should be given with meals)
- o Variability in the enzyme content of the pancreatic replacement or loss of potency of the enzyme (inadequate amount of enzymes)
- o Inactivation of the enzymes by gastric juices or by sunlight.

Hypersensitivity to pancreatic enzymes has been reported in patients who have hypersensitivity to pork proteins. Hyperuricosuria may occur in patients receiving high doses of pancreatic extracts, although recent reports have questioned this relationship. There appears to be a relationship between urinary urate concentration and the severity of pancreatitis. It appears that oral pancreatic enzymes may bind to folic acid, thereby impairing its absorption, but the clinical significance of this is not clear. Fat-soluble vitamins (e.g., vitamins A and E) are poorly absorbed when steatorrhea exceeds 20 g of fat loss per day. Vitamin K is also malabsorbed, but bleeding is rare. Malabsorption of vitamin B$_{12}$ occurs up to 40% of patients with chronic pancreatitis, although vitamin B$_{12}$ deficiency is rare. This malabsorption is thought to be due to the failure of R factor to cleave from the vitamin B$_{12}$-intrinsic factor complex, resulting in failure to absorb vitamin B$_{12}$. Thus, multiple and lifelong vitamin supplementation may be necessary in these patients.

If a patient is found to have chronic pancreatitis relating to autoimmune pancreatitis disease management involves the use of glucocorticoids. There are no clear recommendations for glucocorticoid dose, although 30 to 40 mg of prednisone orally per day for four to eight weeks is reasonable. Repeat pancreatic imaging at one month to assess response. Once a response is observed, predisone is tapered. Normalization of IgG4 may not be apparent for several months, although decreases may be seen within four weeks. Between 30% and 40% of patients experience a relapse after glucocorticoid therapy. If so, a repeat course of prednisone is

indicated, but patient should be tapered to a lower maintenance dose. Immunodulators, such as azathioprine, have been used in afew steroid-dependent patients with success

5. Pancreatic Cysts

It is important to recognize and to treat pancreatic cysts to relieve the patient's symptoms, and to remove any premalignant conditions. While there are many causes of cystic or cyst-like lesions in the pancreas (Table 14), the cystic lesions of major interest and concern are serous, mucinous, intrapapillary mucinous tumour (IPMT) and pseudocyst (Table 15 and 16).

Table 14. **Classification of cystic and cystic-appearing lesions of the pancreas**

➤ Congenital true cysts
  o Polycystic disease
  o Von Hippel-Lindau disease
  o Cystic fibrosis
  o Dermoid cysts

➤ Inflammatory
  o Pseudocysts
  o Abscess
  o Hydatic cyst

➤ Angiomatous cysts

➤ Cystic neoplasms
  o *Mucinous tumors*
    – Mucinous cystadenoma (macrocystic adenoma) and cystadenocarcinoma
    – Intraductal mucin hypersecreting neoplasm; "Mucinous ductal ectasia"
  o *Non-mucinous tumors*
  o Serous cystadenoma (microcystic adenoma)
    – Papillary cystic tumor
    – Cystic cavitation of pancreatic adenocarcinoma or lymphoma

➤ Acquired cysts
  o Central cavitary necrosis
  o Pseudocyst
  o Parasitic cyst

➤ Misdiagnosed non-pancreatic lesions
  o Splenic artery aneurysm
  o Choledochal cyst
  o Mesenteric cyst
  o Duodenal duplication cyst or diverticulum
  o Lesser sac biloma
  o Lymphangioma
  o Hypoechoic solid tumor

➤ Metastases, with cystic component

Printed with permission: Degen L, et al. *Best Practice & Research Clinical Gastroenterology* 2008; 22(1): page 92.

Table 15. <u>Characteristics of p</u>~~P~~ancreatic serous cystadenoma (SCA), mucinous cystadenoma (MCN), IPMT (Intraductal papillary mucinous tumor) and pseudocyst (PC) ~~from the perspective of patient age, gender, alcohol use, pancreatic history, location, malignant potential, as well as locularity and presence of calcifications.~~

Characteristic	SCA	MCN
o Sex	- Female (2-3:1)	- Female (~100%)
o Age	- 60s	- Adenocarcinoma (50s-60s)
		- Carcinoma (60s-70s)
o Ethanol abuse	- No association	- No association
Pancreatic history	- Yes (uncommon)	- Yes (uncommon)
Malignant potential	- No (rare)	- Yes
o Location	- Evenly distributed body/tail	- Body/tail
o Locularity	- Multiple small	- multilocular
o Calcifications	- Yes (central sunburst or stellate)	- Yes (peripheral, curvilinear)

	IPMT	PC
o Sex	- Male (3-4:1)	- Male
o Age	- 60s	- Variable
o Ethanol abuse	- no association	- Yes
o Pancreatic history	- yes (uncommon)	- Yes (uncommon)
o Malignant potential	- yes	- No
o Location	- head	- Head
o Locularity	- multilocular	- Unilocular
o Calcifications	- no	- No, unless associated with chronic pancreatitis

Adapted from: Scheiman JM. *AGA Institute Postgraduate Course* 2006: page 586.

Depending upon the type of cyst and their location in the pancreas, cysts may be treated by continued monitoring, drainage or pancreatic resection (Table 16).

Table 16. **The therapeutic approach (monitor, drain, resect) for cystic lesions in the head, body, and tail of the pancreas**

	Mucinous	Malignant	Serous	Pseudocyst
➢ Head	Monitor	Resect	Monitor	Drain
➢ Body	Resect	Resect	Monitor	Drain

➢ Tail   Resect   Resect   Resect   Resect

Printed with permission: Brugge WR. *2008 ACG Annual Postgraduate course book*: page 270.

65. Carcinoma of The Pancreas

The incidence of cancer of the pancreas has increased steadily over the past 25 years. In males it is the fourth commonest cancer causing death, exceeded only by cancers of the lung, colon and rectum, and prostate. In females it is the fifth commonest cause of death, with only cancers of the breast, colorectum, lung, and ovary/uterus being more frequent. The incidence is higher in males, with a sex ratio of two males to each female; peak incidence occurs in the fifth through seventh decade.

The overall five-year survival rate is less than 3%, and most patients who develop carcinoma of the pancreas die within six months of diagnosis. The poor prognosis in this condition is secondary to the inability to diagnose the carcinoma at an early stage. When symptoms present, the tumor is far advanced and often has metastasized to regional lymph nodes and to adjacent and distant organs, as shown in Table 17.

Table 17. **Most common sites of metastases from pancreatic carcinoma**

- o Local nodes
- o Liver
- o Peritoneum
- o Adrenal glands
- o Lung
- o Kidneys
- o Spleen
- o Bone

Ductal cell adenocarcinoma accounts for 90% of pancreatic tumours. Approximately 5% of pancreatic carcinomas are of islet cell origin; the rest consist of cystadenocarcinoma, giant cell carcinoma and epidemoid carcinoma. The head of the pancreas is the most common site of involvement, accounting for 70% of the cases, whereas the body and tail account for 20% and 10% of the cases, respectively. Hereditary pancreatitis appears to carry a 40-fold increased risk of developing pancreatic cancer by 70 years of age; the risk seems to be associated with a paternal mode if inheritance.

Several etiological agents have been invoked in the pathogenesis of pancreatic carcinoma (Table 18), although most of the studies have not yielded consistent results. Epidemiologically, long-term cigarette smoking is a well-established risk factor. Two tobacco-specific nitrosamines have been proposed as causative agents in the pathogenesis of carcinoma. Little is known of the role of the pancreas in the metabolism of carcinogens involved in exocrine pancreatic carcinoma. High-fat or high-protein diets tend to stimulate CCK release from the duodenum, which in turn can cause pancreatic hypertrophy and may predispose to carcinoma, although the evidence is not convincing. Diabetics are at twice the risk of developing carcinoma of the pancreas as the general population. The mechanism of this is not known. There is no evidence to suggest that alcoholic chronic pancreatitis predisposes to carcinoma. A recent study has shown a four- to five-fold increase in pancreatic carcinoma in individuals exposed to DDT (dichlorodiphenyltrichloroethane). Some epidemiological studies have suggested an increased rate of pancreatic carcinoma in patients who drank chlorinated water; this remains to be proven.

A. B. R. Thomson and E. A. Shaffer

Table 18. **Putative causes/associations of pancreatic cancer**

➢ Hereditary pancreatitis
  o Cationic trypsinogen (CT)
  o CF
  o SPINK

➢ Polyp syndromes
  o FAP
  o HNPCC-Lynch mismatch MLH1, MSH2, BRCH2
  o HNPCC
  o Peutz-Jeghers syndrome
  o Cowden syndrome

➢ Genetic abnormalities
  o Familial atypical mole and multiple melanoma (FAMMM): germline p16 mutation
  o Hereditary breast cancer: germline BRCA2 mutation
  o Oncogenes - K-RAS mutations (90%) and p53 (70%) indicate tumor induction by exogenou
    carcinogens
  o Inactive tumor suppression gene (p59, p16 [DKN2A])
  o Familial pancreatic cancer
  o Familial ovarian and breast cancer

➢ Drugs/Diet
  o Risk factors are smoking, alcohol, and high-saturated fat/low vegetable/low vitamin diet
  o 7-fold increased risk after exposition to dichlorodiphenyltrichloroethane or deviates (e.g.
    ethylene)

➢ Metabolic
  o Chronic pancreatitis
  o Diabetes
  o Partial gastrectomy

➢ Miscellaneous
  o Diabetes mellitus
  o Cystic fibrosis
  o Fanconi anemia
  o Familial adenomatons polyposis
  o Ataxia telangiectasia
  o Neurendocrine tumors

Adapted from: Keller J, et al. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): page. 522.

Genetic defects such as K-ras oncogene, and tumor-suppressor genes including p16, DPC4 and p53 have been proposed to be involved in the patho—genesis of pancreatic carcinoma. Attempts to use the presence of these gene mutations in the diagnosis of occult pancreatic carcinoma seem to be vulner—able to a high false-positive rate.

65.1 Clinical Manifestations

The major symptoms of pancreatic carcinoma include pain, jaundice and weight loss. Rapid and progressive weight loss is probably the commonest symptom of carcinoma of the pancreas, and is not related to the location or to the extent of the tumor.

Most (up to 90%) of the patients suffer from pain during the course of the disease. The pain frequently is a dull aching or boring. Located in the epigastrium, it radiates to the back and increases in severity at night. Depending on the site of the tumor, the pain may radiate to the right or left upper quadrant. Unrelenting pain results from retroperitoneal extension, with invasion of the neural plexuses around the celiac axis.

Jaundice may be the presenting symptom in up to 30% of the patients, and the incidence increases as the disease progresses. It may be associated with pain and pruritus. Jaundice is more common when the head of the pancreas is involved, but obstruction or jaundice can occur secondary to spread to the liver or to lymph nodes around the bile duct. Other nonspecific symptoms include bloating, nausea and vomiting, weakness and fatigue, and diarrhea.

65.2 Signs

The commonest finding in carcinoma of the head of the pancreas is jaundice, with abdominal tenderness and an enlarged liver. Less common signs include a palpable gallbladder, an abdominal mass, and edema. Thrombophlebitis occurs in less than 10% of the patients.

Figure 8. Pancreatic head carcinoma. Transverse sonogram shows the confluence of splenic vein and portal vein. The pancreatic body and tail are normal. The head is enlarged and bulbous with an abnormal texture, appearing hypoechoic on the image.

The development of diabetes in a middle-aged man or elderly patient with no family history of diabetes should suggest pancreatic carcinoma, especially when this is associated with abdominal pain or weight loss.

65.3 Diagnostic Evaluation

Laboratory tests are often normal or nonspecific. Serum alkaline phosphatase and bilirubin are ~~evaluated~~ elevated when the bile duct is obstructed or there are hepatic metastases. Serum amylase may be moderately elevated but also may be normal. Pancreatic secretory studies are not often helpful, since findings overlap with those of chronic pancreatitis.

Several tumor markers have been detected in the sera of patients with pancreatic carcinoma. CA19-9 is the most widely studied pancreatic tumor marker. Its importance and significance in the management of pancreatic cancer are unclear. This marker may be useful as an adjunct in the diagnosis, selection of therapy and postoperative follow-up of patients with pancreatic cancer. Other serum markers include pancreatic oncofetal antigen (POA), α-fetoprotein (AFP), carcinoembryonic antigen (CEA), and pancreatic cancer-associated antigen. These tests are nonspecific and not sensitive enough for screening purposes. Cytologic specimens can be obtained by percutaneous needle aspiration under ultrasound or CT guidance and by aspiration of duodenal or pancreatic juices at ERCP or EUS. Positive cytology may guide further management; on the other hand, negative cytology does not rule out the disease.

Ultrasonography is the initial procedure of choice for detecting pancreatic cancer (Figure 8). However, its usefulness is dependent on the examiner's expertise. Examination may be less than optimal in the presence of increased bowel gas. The sensitivity of this test in pancreatic cancer is reported to be 76–94%, with a specificity of 96%. Once a lesion is detected, a guided biopsy may be helpful in establishing the diagnosis. When obstructive jaundice is present, ultrasound may reveal the presence of hepatic lesions or obstruction of the biliary tree. This procedure is simple and involves no radiation exposure.
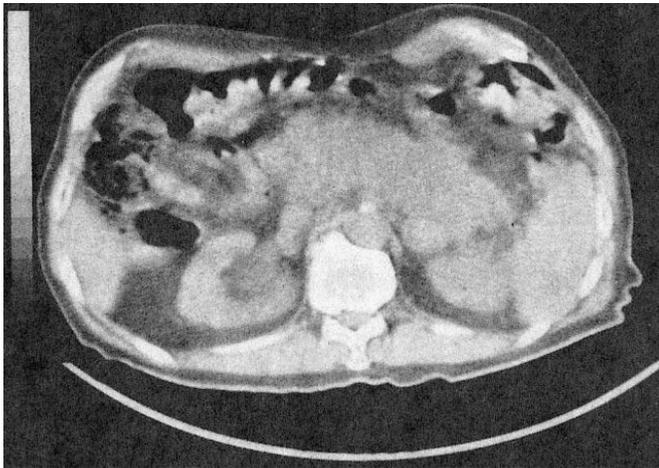
Figure 9. Computerized tomography showing a cancer in the head and body of the pancreas. The tumour is overlapping the superior mesenteric artery posteriorly.

CT is more accurate and gives more information than ultrasonography for diagnosis and staging pancreatic carcinoma (Figure 9). In contrast to ultrasonography, with this technique bowel gas does not interfere with the resolution. Unfortunately, CT has limitations in detecting

early small cancer and small metastases to lymph nodes, liver and peritoneum. Helical CT scan, a newer diagnostic modality, has the capability of producing precise images of the major pancreatic vessels (celiac, superior mesenteric arteries and their branches, and the superior mesenteric veins and their tributaries). This technique detects vascular involvement with great accuracy, hence predicting tumor– resectability and retroperitoneal invasion (Figure 10). A guided biopsy of the lesion

is also possible. Endoscopic ultrasonography (EUS) in combination with guided fine-needle aspiration has may become a useful tool in the evaluation of focal pancreatic lesions. Its overall accuracy in detecting parenchymal lesions and lymph node involvement is about 84%.

When there is a clinical suspicion of a pancreatic lesion and the ultrasound or CT scan is normal, an ERCP is helpful. It has the advantage of combining gastroduodenoscopy, cholangiography and pancreatography. The papilla may also be examined and cytologic sampling may be obtained. When obstruction is present, therapeutic drainage via stents may be attempted. Angiography is no longer used for diagnosing pancreatic carcinoma, but is still useful to evaluate patients who have known carcinoma for resectability, outlining vas—cular anatomy. Newer diagnostic tools such as endoscopicEndoscopic ultrasound may further improve selection of patients who might benefit from curative surgery. Magnetic resonance imaging has no apparent advantage over CT.

Figure 10. Pancreatic adenocarcinoma in the head with direct invasion into the superior mesenteric vein (Courtesy of Dr. A. Hanbridge).

65.4 Treatment

For localized cancers, surgical resection alone, such as pancreatectomy or pancreatoduodenal resection, offers the potential for long-term survival. Unfortunately, at the time of presentation, 75–80% of patients have an unre—sectable tumor. Despite this

intervention, the disease carries a poor long-term prognosis, with a survival rate of 3% at five years. Factors that lead to a poor prognosis in pancreatic carcinomas include the presence of tumor in the lymph- nodes and neural tissues, vascular invasion, tumor encasement of celiac or superior mesenteric artery, tumor size greater than 2.5 cm and histologically poorly differentiated

tumor. Pancreatic surgery using the Wwhipple procedure should be done only in specialized centers where such an operation is performed by a small number of highly trained surgeons.
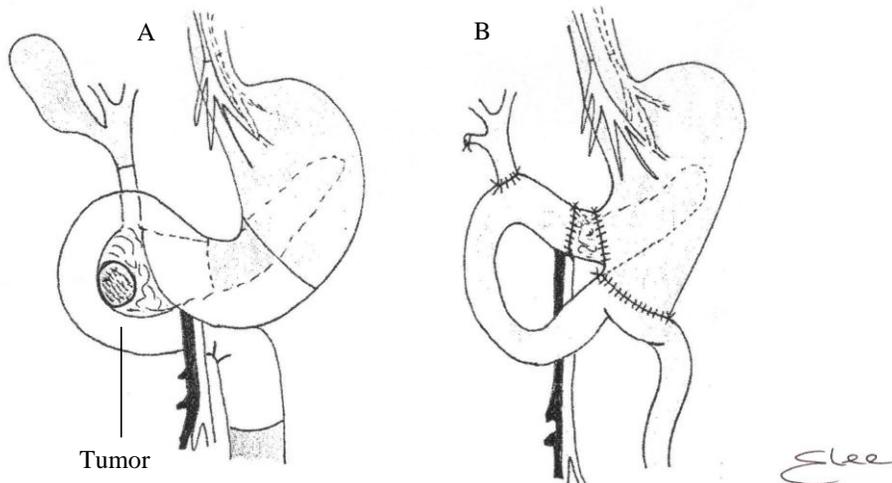
A. o An en bloc resection of the distal stomach, duodenum, common duct, and head of the pancreas containing the pancreatic neoplasm is performed (areas removed are not shaded).
   o A cholecystectomy and truncal vagotomy are also done.

B. o Gastrointestinal continuity is restored by performing a pancreaticojejunostomy, a choledochojejunostomy, and a gastrojejunostomy.

Adapted from: Reber, H.A and Way, L.W: The pancreas. In Dunphy, J.E, and Way, L.,W [eds.]. *Current Surgical Diagnosis and Treatment*, 3rd Ed. Los Altos, Calif. Lange Medical Publications, 1977.

In such centers the mortality rate approaches 6%, as compared to nonspecialized centers where the mortality rate reaches 28%. The five-year survival rate in some recent studies appears encouraging.

Complications can occur in up to 20% of patients following pancreatoduo—denectomy. These include delayed gastric emptying (20%), pancreatic fistula (14%), wound infection (10%), pancreaticojejunal leak, intra-abdominal sepsis, biliary anastomotic leak, gastrointestinal bleeding and other intra-abdominal hemorrhage. Factors favoring longer survival include jaundice at presentation, a small tumor mass, early tumor stage and a well-differentiated tumor. Palliative operations for unresectable tumor, such as alleviating biliary or duodenal obstruction, offer some relief. Surgery is frequently associated with high morbidity and mortality; hence,

nonsurgical intervention may be preferable. Biliary obstruction can be relieved by percutaneous drainage or by endoscopic stenting of the bile duct. Unfortunately these stents tend to occlude and may require frequent changes.

Adjuvant chemotherapy in combination with radiotherapy, ~~such as with~~ (5-fluorouracil (5-FU), has shown minimal effect in long-term survival.~~Recently a new chemotherapeutic agent, gemcitabine, has shown similar results to 5 FU in terms of response rate and survival, with more tolerable side effects.~~ Irradiation therapy has been advocated in treating larger tumors it may offer local control and pain management, although its benefit in long—term survival has not been proven.

For palliative chemotherapy of pancreatic cancer, Gemcytabine has shown a small stastically significant benefit over 5FU in overall survival, and an approximate 15% improvement in one year survival for advanced pancreatic cancer. It is the recommended palliative chemotherapy in advanced pancreatic cancer.

76. Pancreatic Islet Cell Tumors

There are numerous types of pancreatic neuroendocrine tumors (Table 19). The most common of these rare tumors is insulinoma and gastrinoma, with an annual incidence of approximately $1/10^6$. The rate of malignancy is over 50% in these pancreatic islet cell tumors, except for insulinoma (~10%) and Grfoma (>30%).

Table 19. **A comparison and contrast of the incidence, symptoms and signs, rate of malignancy, hormone causing symptoms and signs, and frequency of ~~MEN-1~~Multiple Endocrine Neoplasia (MEN-1) in insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma, GRFoma ACTHoma and PEToma**

Tumor syndrome	Primary symptoms/signs (approximate frequency, %)
➢ Insulinoma	o Hypoglycemic symptoms (100)
➢ Gastrinoma, Zollinger-Ellison syndrome	o Abdominal pain (75) o Diarrhea (65) o Dysphagia/pyrosis GERD (20)
➢ VIPoma, (Verner-Morrison syndrome, WDHA, pancreatic cholera)	o Diarrhea, dehydration (100) o Hypokalemia (95) o Hypochlorhydria (30) o Flushing (20)
➢ Glucagonoma	o Dermatitis (80) o Weight loss (70) o Diarrhea (15)
➢ Somatostatinoma	o Diarrhea (70)
➢ GRFoma	o Acromegaly o Abdominal pain

- ➢ ACTHoma
  - ○ Cushing's syndrome

- ➢ PTHoma causing: hypercalcemia
  - ○ Malignant tumor
  - ○ Hypercalcemia

Tumor syndrome	Primary symptoms/signs (approximate frequency, %)
➢ Carcinoid syndrome	o Diarrhea
	o Flushing
➢ PEToma (secreting: rennin)	o Hypertension
➢ Erythropoietin	o Polycythemia

Abbreviation: GRF, growth hormone releasing factor.

Adapted from: Jensen, Robert T and Horton, Jeffrey A. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: 626.

Pancreatic islet cell tumors are divided into two types: (1) an endocrine type that elaborates excessive gastrointestinal tract hormones, causing specific clinical syndromes, and (2) a nonfunctioning type that is characterized by symptoms related to the size, location and invasion of the tumor mass. Patients with multiple endocrine neoplasm type 1 (MEN-1) and von Hippel-Lindau disease (VHL) are predisposed to develop pancreatic endocrine tumors. Pancreatic islet cell tumors have a better prognosis than those associated with ductal cell adenocarcinoma. They may be diagnosed by the classic clinical manifestation, by the detection of hormones in the serum and by dynamic CT scan with intravenous and oral contrasts.

Several pancreatic islet cell tumors have been identified. These tumors tend to elaborate a variety of biologically active peptides, resulting in a variety of clinical presentations. These peptides include glucagon, insulin, gastrin, vasoactive intestinal peptide (VIP), somatostatin and pancreatic polypeptide (PP).

Insulinoma is the most common neoplasm of the endocrine pancreas. The insulinoma syndrome is associated with Whipple's triad, which includes symptoms of (1) fasting hypoglycemia (confusion, seizures, personality changes, in addition to palpitation, tremulousness and diaphoresis), with (2) a low serum glucose level, and (3) a relief of symptoms by the administration of glucose. The diagnosis can be made by the demonstration of high serum insulin and low blood sugar, and an elevation in the insulin-to-glucose ratio (IG). The tumor may be localized by dynamic CT scan. Treatment includes surgery to remove the tumor if it is well localized or amenable to surgery, and ~~a combination chemotherapy including streptozocine, doxorubicin and 5-fluorouracil.~~ prior to that, diet and medical therapy with diazoxide or octreotide to combat hypoglycemia.

Glucagon-secreting tumors (*glucagonomas*) arise from the alpha cells of the pancreas. Patients commonly present with mild diabetes, dermatitis, delayed gastric emptying, stomatitis, ileus and constipation. The dermatitis is manifested by a skin rash termed *necrolytic migratory erythema*, commonly appearing over the lower extremities. The diagnosis is established by the demonstration of elevated plasma glucagon levels that increase, paradoxically, with challenge by intravenous tolbutamide. Glucagonoma tends to present with large tumors and can be demonstrated by dynamic CT scan.

Gastrin-secreting tumors (*gastrinomas*; Zollinger-Ellison syndrome) arise from nonbeta islet cells. They are frequently malignant and tend to be multiple. They commonly present with recurrent severe peptic ulceration accompanied by marked gastric acid hypersecretion and occasionally diarrhea. The diagnosis is established by the demonstration of marked fasting

hypergastrinemia and marked gastric acid hypersecretion. In patients who have borderline increases in gastrin, provocative testing with secretin is indicated. Following secretin stimulation, gastrin levels increase in patients with gastrinoma, whereas in patients with common duodenal ulcer, gastrin levels may show a minimal increase, a decrease or no change. High levels of gastrin may be present in a condition known as G-cell hyperplasia. This can be distinguished from gastrinoma by the sharp rise in gastrin level (> 200%) in response to meals. Patients with gastrinoma show minimal or no rise in gastrin level.

Vasoactive intestinal peptide-secreting tumors (*VIPoma*; Werner-Morrison syndrome) produce the pancreatic cholera syndrome, which is characterized by severe diarrhea, hypokalemia and hypochlorhydria or achlorhydria. Fluid secretion may exceed 3–5 L, with a loss of 200–300 mEq of potassium daily. Although the diagnosis is established by the demonstration of high levels of VIP, other substances, such as prostaglandins and secretin-like substances, may contribute to this syndrome.

Somatostatin-producing tumors (*somatostatinomas*) are the least common of pancreatic islet cell tumors, so by the time of diagnosis they tend to be malignant and have usually metastasized. They commonly present with mild diabetes mellitus, gallstones with a dilated gallbladder, anemia, hypochlorhy—dria and malabsorption. The diagnosis is established by the demonstration of high serum levels of somatostatin.

Pancreatic polypeptide-producing tumors have not been shown to produce any clinically defined syndrome.

76.1 Treatment

Pancreatic endocrine tumors are ideally treated by resection. Unfortunately, despite all our available techniques, up to 40% of these tumors tend to escape localization. These tumors tend to be single or multiple and may be located in any portion of the pancreas or ectopically in the duodenum or any other part of the gastrointestinal tract. ~~It appears that endoscopic ultrasonography may play an important role in tumor localization, but this technique is operator dependent and is not widely used.~~

~~Recently~~ Both octreotide scintigraphy, and more recently, endoscopic ultrasound ~~ha~~ves shown promise in detecting endocrine islet cell tumors, which appear to have somatostatin receptors. ~~Radiolabeled~~ In octreotide scintigraphy, radiolabeled somatostatin analogues bind to these receptors and can be demonstrated by gamma camera scintigraphy. This test offers some hope in differentiating endocrine versus ductal cell tumors. It may assist the surgeon in delineating and removing the tumor and possibly the metastatic lesions.
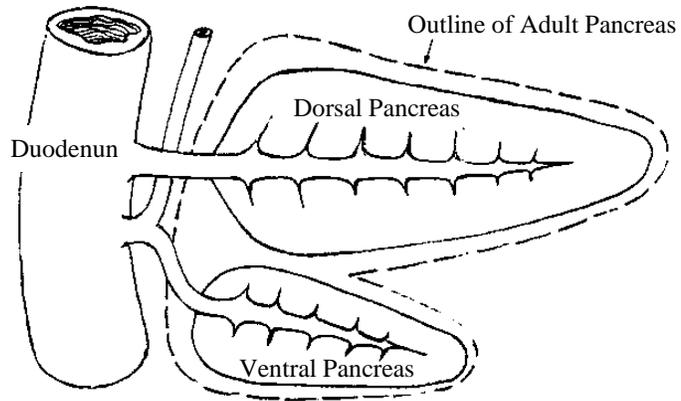
Figure 11. Pancreas at approximately 7 weeks fetal life.

87. Pancreatic Divisum

Pancreas divisum is the most common variant of human pancreas, occurring in nearly 10% of the population. This anomaly results from the failure of fusion of the dorsal and ventral pancreatic ducts, which usually occurs in the second month of fetal life. This results in the drainage of the main pancreatic duct (including the superior-anterior aspect of the head, the body and the tail) into the dorsal duct via the accessory papilla. The ventral duct, which drains the posterior-inferior aspect, joins the common bile duct and empties into the major papilla (Figure 11). The diagnosis of this condition is made by ERCP.

Most patients having this anomaly are symptom-free, although some reports have suggested a high incidence of abdominal pain and pancreatitis. It has been suggested that the relative stenosis of the accessory papillary orifice, the major outflow tract for pancreatic secretions, is the cause of problems.

Endoscopic minor papilla sphincterotomy as well as~~or~~ dorsal duct stent placement have been studied and shown promise as therapy for this developmental anamoly. ~~transduodenal sphincteroplasty has been advocated as the operation of choice in these individuals. The results obtained with this intervention have been controversial. Some studies have reported a success rate of 90% in patients with pancreas divisum pancreatitis after two years, whereas other reports did not support such findings. From the available literature, surgical intervention in pancreas divisum is as controversial as its causative relationship in abdominal pain and pancreatitis.~~

9. Cystic Fibrosis in The Adult

Cystic fibrosis (CF) is no longer solely a pediatric disease. CF is the most common potentially lethal genetic disease affecting Caucasians. Its incidence shows regional variations, but overall incidence in Caucasians is approximately 1 per 2,500 live births; it is inherited as an autosomal recessive trait. CF is also the most common cause of chronic lung disease and pancreatic insufficiency in patients under the age of 20. It is practically unknown among North Americans of African origin, with an incidence of less than 1 in 99,000 among ~~Orientals~~Asian Americans.

Over the past decade the fundamental biochemical defect in CF has been identified. The gene has been cloned and up to 300 alleles have been discovered. The gene product is a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) and is present on the long arm of chromosome 7. This regulator, the main chloride transport system, is defective in individuals with CF. The regulator is synthesized within the epithelial cell, then transported to the apical cell membrane of the epithelial duct cells of the proximal pancreatic duct. The commonest mutation in CF is that of a three-nucleotide base pair deletion that results in a missing phenylalanine at position 508 in the first nucleotide binding fold. This mutation is often referred to as delta F508. Its main function is to act as a chloride channel that is activated through cAMP-mediated phosphorylation, thus allowing secretion of chloride ions into the pancreatic duct or to the skin through the sweat glands. In addition to CFTR, these cells contain Cl^-/HCO_3 exchangers, which are responsible for bicarbonate secretion and are dependent on luminal chloride, which is supplied by cAMP-activated chloride channels. Thus, in CF, altered chloride secretion results in decreased bicarbonate produc-tion and ultimately failure to adequately hydrate and alkalinize the concentrated protein secretions of the acinar cells. This proteinaceous material becomes inspissated, resulting in ductal obstruction and ultimately acinar cell destruction, fibrosis and

malabsorption. The decrease in bicarbonate secretion also results in failure to neutralize duodenal acid, thus leading to further malabsorption by decreasing lipase activity and altering the bioavailability of enteric-coated enzyme supplement.

The "classic" picture of a chronically malnourished child with progressive lung disease and pancreatic dysfunction culminating in early death is an oversimplification. CF should now be regarded as a syndrome with a heterogeneous assortment of presentations involving variable degrees of organ dysfunction and damage. Pulmonary disease and its complications still dominate the clinical picture in most patients, and are the primary determinants of overall morbidity and mortality. However, as many as 20% of CF patients are not diagnosed until after the age of 15 because they have atypical presentation (e.g., recurrent sinusitis, nasal polyps, chronic bronchitis, recurrent abdominal pain, loose, foul-smelling stools, cirrhosis and infertility).

The advent of vigorous physiotherapy, more effective antibiotics, improved pancreatic extracts and continuing care in specialized CF clinics has resulted in a median survival of at least 18 years. Indeed, in many CF centers, half the patients survive 26 years, and up to 90% of patients may live more than 18 years after the diagnosis has been made. With such increased survival, gastrointestinal complications are becoming increasingly common.

Abnormalities have been identified in glycoproteins, mucus secretions, circulating proteases and cell transport mechanisms. Liver and biliary tract disease may occur in individuals with CF. The incidence of biliary cirrhosis reaches 14% during the second decade of life in those who have pancreatic insufficiency. In these individuals subclinical hepatic involvement, manifested as biochemical or ultrasound abnormalities of the liver, is common. High losses of sodium and chloride through sweating during periods of heat in the summer months can lead to sodium depletion, dehydration, cardiovascular collapse and death. The abnormally thick mucus produced obstructs ductules and tubules, and results in distal organ damage, which leads to chronic obstructive lung disease, pancreatic insufficiency, hepatic fibrosis and intestinal obstruction. The mucosal and submucosal glands of the small intestine are dilated, with acidophilic concretions. Steatorrhea and enteral protein loss result from exocrine pancreatic failure, low duodenal pH and perhaps also impaired absorption of fatty acids. These patients require supplementation with fat-soluble vitamins A, D, E and K.

Abdominal pain is common in CF patients. It may be related to steatorrhea, constipation, meconium ileus equivalent, intussusception, cholelithiasis, duodenal ulcers or pancreatitis. In contrast to infants and children, adults are less affected by malabsorption, although close questioning may reveal that they experience cramps, flatulence and frequent, greasy, foul-smelling, bulky stools.

8.1 Complications

There are a number of gastrointestinal, hepaticopancreaticobiliary as well as non-GI manifestations of cystic fibrosis (Table 20). Most CF patients have height and weight levels that are less than the mean for their age and sex. Although during adulthood nutritional status declines progressively with advancing age, not all patients are malnourished at the time of diagnosis or in early adulthood. In early adulthood, some 10% of patients are above the 90th percentile, while others are even overweight.

Table 20. GI and Hepatobiliary clinical manifestations of CF

- Gastrointestinal
  - Gastroesophageal reflux
  - Peptic ulcer disease
  - Fat malabsorption
  - Mecomium ileus
  - Volvulus
  - Ileal atresia
  - Distal intestinal obstruction syndrome (meconium equivalent)
  - Fecal masses
  - Intussusception
  - Constipation
  - Impaction
  - Rectal prolapse
  - Hemorrhoids
  - Peritonitis

- Pancreas
  - Nutritional failure caused by pancreatic insufficiency
  - Diabetes
  - Calcification
  - Maldigestion
  - Fat soluble vitamin deficiencies
  - Steatorrhea and azotorrhea

- Hepatobiliary
  - Mucus hypersecretion
  - Gallstones, atrophic gallbladder
  - Focal biliary cirrhosis
  - Cirrhosis
  - Portal hypertension
  - NAFLD
  - Hepatomegaly
  - Premature death

Non-GI/Hepatobiliary manifestations of cystic fibrosis in the adult.

- Respiratory
  - Sinusitis
  - Nasal polyposis (secondary to mucous membrane hypertrophy)
  - Lower respiratory infections
  - Bronchiectasis

- ➢ GU
  - o Male infertility (sterility; congenital absence of vas deferens, epididymis, and seminal vessels)
  - o Female infertility (increased viscosity of vaginal mucous)

- ➢ Nutrition
  - o Clubbing
  - o Short stature

- ➢ Premature death

- ➢ Reproductive
  - o Female gender
    - − Increased viscosity of vaginal mucus and decreased fertility
  - o Male gender
    - − Sterility: absence of ductus deferens, epididymis and seminal vesicles

- ➢ Skeletal
  - o Retardation of bone age
  - o Demineralization
  - o Hypertrophic pulmonary osteoarthropathy

- ➢ Ophthalmic
  - o Venous engorgement
  - o Retinal hemorrhage

- ➢ Other
  - o Salt depletion through excessive loss of salt via the skin
  - o Heat stroke
  - o Hypertrophy of apocrine glands

There is no correlation between the patient's nutritional status and the severity of the steatorrhea or gastrointestinal symptoms, or age at diagnosis. The height and weight attained seem to correlate only with the severity of the pulmonary disease; those individuals with the least pancreatic insufficiency tend to have better preservation of pulmonary function.

Pancreatic insufficiency markedly overshadows the other GI complications of CF. In spite of the clinical impression of a voracious appetite, overall energy intake in the CF patient is usually inadequate. Maldigestion and malabsorp—tion, along with the increased energy requirements associated with pulmonary disease, further compound the energy problem.

CF patients also show biochemical evidence of essential fatty acid deficien—cy. Improvement may be achieved with oral linoleic acid monoglyceride or with total parenteral nutrition. Essential fatty acid deficiency is associated with impaired intracellular oxygenation, decreased membrane fluidity and impaired transport mechanisms. It has not yet been established, however, what benefit will be derived by treating and preventing essential fatty acid deficiency.

In addition to the problems of essential fatty acid and energy deficiency, there is a third major problem in the nutrition of the CF patient: deficiency of fat-soluble vitamins. Even with a standard supplementation of vitamin A 4,000 IU/day, vitamin A levels, retinol binding protein levels and serum carotene may remain low. Approximately 25% of patients have evidence of vitamin D deficiency. Otherwise, the management of pancreatic insufficiency in adults with CF is similar to the management of pancreatic insufficiency due to other conditions. About half of the adults with CF show some degree of glucose intolerance. Diabetes mellitus ~~is easy to control~~in this instance is controlled with insulin, and~~;~~ because glucagon levels are decreased, ketoacidosis is extremely uncommon. The presumed pathogenesis of the pancreatic islet cell dysfunction is fibrosis-induced islet cell disarray and strangulation.

Meconium ileus is seen in approximately 10% of neonates with CF and is primarily related to the secretion of abnormal mucinous (glycoprotein) mate–rial by the intestinal glands. Children, adolescents and adults have a counter–part, termed *meconium ileus equivalent*, that is characterized by recurrent episodes of intestinal obstruction. Typically, there is colicky abdominal pain, a palpable, indentable right lower quadrant mass and evidence of mechanical obstruction. Constipation is considered a milder form of this disorder, and must be differentiated from intussusception, which occurs in a small number of CF patients. There is usually a history of precipitating cause, such as immobilization, use of antidiarrheal agents, dietary indiscretions, or reduction or abrupt discontinuation of oral enzyme therapy.

The diagnosis of meconium ileus equivalent is suggested by the presenta–tion. Plain abdominal radiographs may show an empty colon with bubbly granular material proximally, and ileal distention with air fluid levels. It is necessary to confirm the diagnosis by early fluoroscopy guided Gastrografin® enema studies because of the high mortality of this condition and the need to rule out intussusception. Nasogastric suction and correction of electrolyte imbalance result in resolution of the obstruction in 80% of cases. Decompressive surgery may be necessary if medical management fails.

Pancreatitis is relatively uncommon in CF patients, but tends to occur in those patients (some 15%) whose pancreatic function is initially normal. The pathophysiology of the pancreatitis is presumably related to precipitation of abnormal secretions in the tubules, with subsequent damage. Biliary tract disease and alcohol are other possible causes of pancreatitis in these patients.

An increase in the incidence of duodenal ulcer might be expected in CF patients because of the loss of pancreatic bicarbonate buffer, but in fact duodenal ulcer is uncommon.

Patients with untreated pancreatic insufficiency commonly have profound malabsorption of bile acids in the terminal ileum and fecal losses of bile acids. This interrupts the normal enterohepatic circulation of bile acids. The etiology of bile acid wastage is unknown, but it probably relates to the presence of steatorrhea, with bile acid binding to undigested fat, fiber and other intraluminal contents. As a result of the excessive fecal bile acid loss, there is a decrease in the total bile acid pool; the bile becomes saturated with cholesterol. Up to 60% of adolescents and adults with CF have gallbladder abnormalities (e.g., cholelithiasis, nonvisualization, microgallbladder, and marginal filling defects or septation). There is a high incidence of both gallbladder abnormalities and abdominal pain in these patients, but there is not necessarily a cause-effect relationship between the cholelithiasis or gallbladder abnormalities and the clinical symptoms. The hazards of surgery must be weighed against the hazards of nonoperative intervention. The structure and function of the gallbladder may be

evaluated by ultrasonography and oral cholecystography.

Treatment of pancreatic insufficiency with oral enzymes will decrease bile acid loss, thus correcting the lithogenic nature of the bile. However, the abnormal glycine:taurine ratio and the preponderance of cholic and chenodeoxycholic acid persist despite enzyme replacement. Ursodeoxycholic acid therapy remains experimental.

With increased age and survival, liver disease is becoming increasingly prevalent in CF patients. The most common hepatic lesion in CF is steatosis, secondary to decreased circulating lipoprotein levels and decreased hepatic triglyceride clearance. Other hepatic lesions seen include nonspecific portal changes, excessive biliary ductal mucus, mild ductal proliferation and focal biliary cirrhosis. A small number of these patients will develop multilobular biliary cirrhosis, the progression remaining clinically silent until portal hyper—tension supervenes with classical presentation of ascites, hypersplenism or variceal bleeding. Hepatic decompensation and portosystemic encephalo—pathy are extremely uncommon because of the relative hepatic parenchymal integrity and the overall focal nature of the pathology. The only clinical clue is the development of a hard, knobby liver, while liver biochemical tests remain relatively normal. The results of therapeutic portacaval anastomoses are encouraging, with no development of portosystemic encephalopathy.

98.2 Diagnosis

Classical CF in infants and children is easy to diagnose. However, diagnosis of CF is more difficult in adults and in mild or atypical cases. The cornerstone of diagnosis is the quantitative pilocarpine iontophoresis sweat chloride test. This should be performed on two separate occasions, using a sample of

100 mg of sweat or more. Chloride levels that are continually above 60 mEq/L are virtually diagnostic. Such levels are not found with other chronic pulmonary or gastrointestinal tract diseases. Sweat chlorides may, however, occasionally reach 60 mEq/L or more in a variety of other disorders, includ—ing untreated adrenal insufficiency, hereditary nephrogenic diabetes insipidus, hypothyroidism, and a variety of genetic mucopolysaccharide disorders.

Sweat chloride testing should be performed in infants and children with chronic pulmonary disease, meconium ileus, steatorrhea, rectal prolapse, failure to thrive, heat prostration or pansinusitis, and in siblings of affected individuals. In addition, children, adolescents and young adults should be screened if they have any type of chronic liver disease, long-standing gastrointestinal complaints, childhood or cryptogenic cirrhosis, aspermia or malabsorption.

98.3 Treatment

Pancreatic enzyme replacement is the mainstay of treatment in patients with CF who suffer from pancreatic insufficiency. Enteric-coated enzymes ideally should be used, since they are not inactivated by gastric acids. Ultimately these enzymes could be used in combination with an H_2 blocker. At least 30,000 USP units of lipase should be administered and taken together with food.

Hyperuricosuria may occur in these patients secondary to the large purine content in the enzyme preparation. This complication can be controlled by decreasing the dose of the enzymes.

648
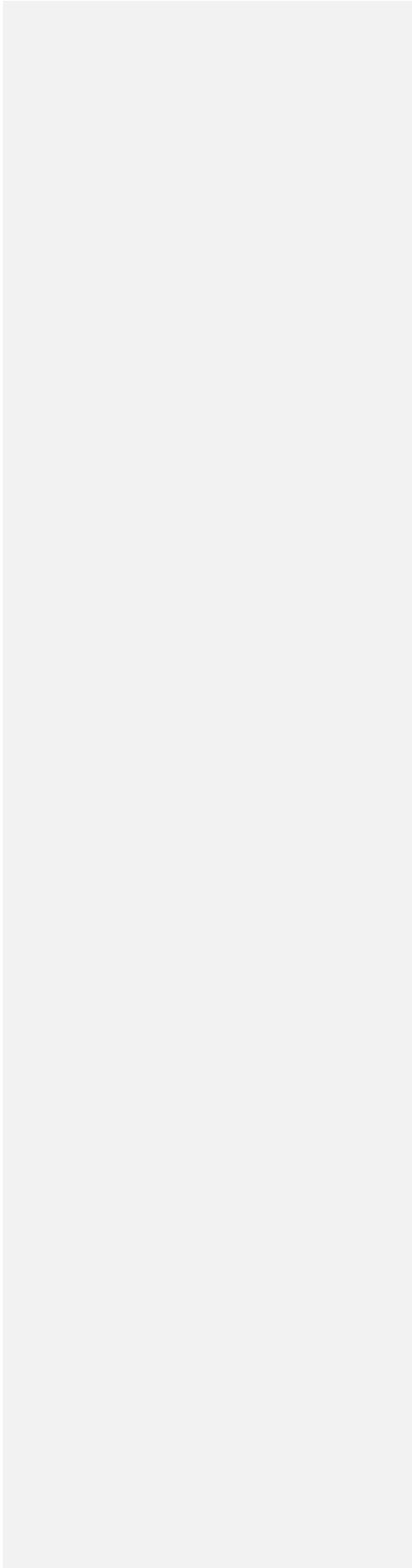
Chapter 33: Nutrition in Gastrointestinal Disease

J.S. Whittaker, J.P. Allard and H.J. Freeman

1. Introduction

Food assimilation is the major function of the gastrointestinal tract. Many gastrointestinal diseases have important nutritional effects. Digestion and absorption of nutrients are discussed elsewhere. This chapter reviews physiologic considerations that are essential for planning proper nutritional management. The focus will be on the role of the liver in regulating the supply of carbohydrate and lipid fuels as well as ensuring the availability of essential substrates to peripheral tissues. The clinical features of malnutrition and specific effects of malnutrition on the gastrointestinal tract and liver will be discussed along with diet therapy in gastrointestinal disease. Finally, an approach to clinical nutrition will be presented, including nutritional assessment and the rational use of enteral and parenteral nutritional support.

2. Essential Physiologic Concepts in Nutrition

To maintain a continuous supply of nutrients in the bloodstream in the face of intermittent dietary intake, a complex set of regulatory mechanisms have evolved. These allow the storage of nutrients during feeding, and their release from storage pools during the interdigestive period so as to maintain nutrient levels in the bloodstream within remarkably narrow limits. Short-term regulation between the fed state and the interdigestive state is mediated principally by (Goldwasser 1997) the concentration of several key substrates and (Klein 2002) a set of regulatory hormones, which include insulin, glucagon, catecholamines and corticosteroids (Table 1).

Table 1. Hormonal regulation of nutrient metabolism

Hormone	Principal metabolic actions
➢ Insulin	o Increases glucose uptake in peripheral tissues
	o Stimulates protein synthesis
	o Inhibits lipolysis and glycolysis
	o Increases amino acid uptake into muscle (particularly important post-exercise)
➢ Glucagon	o Increases cyclic AMP levels in the liver and adipose tissue, with stimulation of fatty acid mobilization, glycogenolysis, glycolysis and gluconeogenesis, thereby increasing plasma glucose
➢ Catecholamines	o Increase cyclic AMP levels in the liver, skeletal muscle and adipose tissue, with release of glucose, free fatty acids and lactate
➢ Corticosteroids	o Increase gluconeogenesis Increase amino acid mobilization from the periphery (chiefly skeletal muscle)
	o Increase fatty acid release from extremities
	o Decrease glucose utilization by peripheral tissues by increasing post-receptor insulin resistance
	o Increase glucagon release

Taken together, the actions of glucagon, catecholamines and corticosteroids work to increase plasma glucose and free fatty acid levels in direct opposition to insulin. Therefore, the release of these hormones, which occurs in response to low glucose levels and/or stress, leads to insulin resistance.

Glucose is rapidly absorbed following ingestion as starch, disaccharides or a monosaccharide. The glucose is transported via the portal system to the liver, which extracts a considerable fraction of

First Principles of Gastroenterology and Hepatology   A. B. R. Thomson and E. A. Shaffer

portal venous glucose. The remainder enters the systemic circulation and causes pancreatic secretion of insulin. The high portal vein insulin and glucose concentrations lead to hepatic glucose uptake with conversion to glycogen and fatty acids. The peripheral rise in insulin, which occurs in association with the rise in plasma glucose concentration, causes a large peripheral uptake of glucose, first by muscle cells, and second by adipocytes. Glucose is the essential substrate for brain, renal medulla and red cell metabolism; other organs mainly use fatty acids for energy. The rise in plasma insulin also leads to amino acid uptake by muscle and has an antiproteolytic effect. These effects on muscle protein have led to the designation of insulin as an "anabolic hormone." In the postabsorptive or interdigestive state, plasma glucose is low, with low plasma insulin levels. The low plasma insulin influences the metabolism of all three macronutrients (i.e., carbohydrates, fat and protein). Glycogenolysis occurs in the liver to maintain plasma glucose levels. The low plasma insulin also allows lipolysis to take place, such that fatty acids can be utilized as the major energy substrate. Finally, the low plasma insulin leads to proteolysis, particularly of muscle protein, which leads to release of alanine and glutamine, which can be used for gluconeogenesis in the liver. This gluconeogenesis occurs in concert with glycogenolysis to ensure an ongoing supply of glucose for the body.

Other hormones, such as glucagon, catecholamines and growth hormone, play less important roles in macronutrient metabolism, but in general have been termed the "stress hormones," since they are released during times of stress and have anti-insulin effects. In particular, if for any reason there is a low blood sugar, all these hormones are released and will promote an elevation in plasma glucose.

The flux of lipid nutrients in the fed and the interdigestive states is contrasted in Figure 2. In the fed state, fat enters the circulation from the intestine as chylomicrons, which are large droplets of triglyceride emulsified by a surface mono-layer of phospholipid and apolipoproteins. Additional apolipoproteins are transferred onto the chylomicrons from HDL. The artificial fat emulsions used for parenteral nutrition are very similar to chylomicrons in that they contain a core of triglyceride with a surface monolayer of phospholipid. They initially contain no apolipoproteins, but acquire these from HDL very rapidly once they have entered the circulation. One of the apolipoproteins, apolipoprotein C-II, is particularly important in that it is an essential cofactor for the action of lipoprotein lipase. This enzyme is attached to the capillary endothelium in tissues, such as the heart and adipose tissue, that are active in utilizing fatty acids. Chylomicrons bind to the enzyme and the core triglyceride is rapidly hydrolyzed. The released fatty acids are then taken up and utilized in the peripheral tissues. As the chylomicron particle shrinks in size, the excess surface material is transferred back to HDL, and ultimately the remnant particles are cleared via a specific receptor in the liver. The process of lipolysis is extremely efficient, and the half-life of chylomicron triglyceride in the circulation is normally less than 15 minutes in the postabsorptive or interdigestive state. Chylomicrons are absent, but triglyceride fuels are available in the circulation in the form of VLDL, which are secreted by the liver. The substrates for triglyceride assembly include free fatty acids released from adipose tissue through the action of a hormone-sensitive lipase, and fatty acids synthesized in the liver from acetyl-CoA. The newly secreted VLDL acquire apolipoproteins and cholesterol ester from HDL. Lipolysis of VLDL in peripheral tissues is mediated by lipoprotein lipase. As the particle decreases in size, free cholesterol transfers to HDL, where it is esterified through the action of lecithin-cholesterol acyltransferase (LCAT), and the resultant cholesterol ester is then transferred back to the lipolyzed particle, where it forms part of the core. When lipolysis is completed, what is left behind is termed an LDL particle. This is smaller and denser than VLDL, has lost all apolipoproteins except apolipoprotein B, and has a core of cholesterol ester rather than

triglyceride. LDL is cleared relatively slowly, with a half-life of several days. The uptake of LDL is mediated by a specific membrane receptor, termed the LDL receptor, whose activity in turn is regulated by intracellular cholesterol levels. The most active tissues (on a weight basis) for LDL clearance are steroidogenic tissues, such as the adrenals, gonads and the liver; because of its size, the liver accounts for over half of total LDL catabolism. As peripheral tissues cannot degrade cholesterol, excess cholesterol is returned to the liver via HDL, where it is used for bile acid synthesis or excreted in the bile.

Starvation leads to a number of adaptive responses. There is a depletion of liver glycogen within 24 to 48 hours, with stimulation of gluconeogenic enzymes to allow the production of glucose from amino acids released through protein breakdown in skeletal muscle. Lipolysis in adipose tissue leads to increased fatty acid levels and activation of enzymes responsible for β-oxidation of fatty acid in the liver (acyl-CoA-carnitine acyltransferase). In addition to acetyl-CoA, fatty acid oxidation generates ketone bodies. One important adaptive response to starvation is the induction of 3-hydroxybutyrate dehydrogenase in the brain, which allows this organ to utilize ketone bodies as a fuel. Decreased dependence on glucose reduces the need for excess gluconeogenesis and spares muscle protein. In a relatively lean 70 kg man with 12% body fat, survival without food can be expected to be about 60 days or longer.

3. Clinical and Laboratory Features of Protein- Energy Malnutrition

Protein-energy malnutrition may result from a number of causes. These are shown in Table 2. Intake or assimilation may be impaired or, alternatively, losses may be increased, as occurs with excessive enteric protein loss in protein-losing enteropathies. In some disorders, multiple causes may be present. Moreover, requirements may be significantly increased in some patients as a result of growth, pregnancy, tissue injury or a superimposed disease process. In some patients with chronic debilitating diseases, multiple factors may be responsible.

Table 2. Causes of protein-energy malnutrition

➢ Impaired intake
  o Insufficient quantity or quality
  o Impaired intake due to systemic disease (e.g., cerebrovascular accident, chronic infections
  o Impaired intake due to localized gastrointestinal disease (e.g., benign or malignant esophageal stricture)
 	
➢ Impaired digestion and/or absorption
  o Selective enzyme defect (e.g., enteropeptidase deficiency, trypsinogen deficiency)
  o Generalized enzyme defect (e.g., pancreatic exocrine insufficiency)
  o Impaired small intestinal assimilation (e.g., celiac disease)
 	
➢ Excessive enteric protein loss
  o Gastric or intestinal mucosal disease (e.g., Ménétrier's disease, intestinal lymphangiectasia)
  o Extraintestinal disease with lymphatic blockage (e.g., pericarditis, lymphoma)
 	
➢ Disorders with multiple causes
  o Advanced malignancy
  o Chronic renal failure with uremia
  o Other chronic debilitating diseases

Malnutrition has been classically divided into kwashiorkor (protein restricted) and marasmus (protein-calorie restricted). In kwashiorkor, the subject ingests a moderate number of calories, usually as complex carbohydrate (e.g., rice), but very little protein. The carbohydrate is absorbed as glucose, causing rises in plasma glucose and insulin, and leading to decreased lipolysis and proteolysis. The liver is therefore supplied with inadequate amino acids, with little oral intake and little peripheral mobilization from skeletal muscle stores. Transport of triglyceride made from ingested glucose is impaired since there is inadequate production of apoprotein, which is needed for the formation of VLDL. The liver becomes fatty and enlarged. Furthermore, other proteins, including albumin, are inadequately produced by the liver in kwashiorkor, and serum albumin falls, with resulting peripheral edema. With marasmus the subject takes inadequate amounts of protein and calories. The low caloric intake means that only small amounts of carbohydrate are taken; plasma glucose and insulin are low. Hence, lipolysis and proteolysis occur, with adequate delivery of amino acids from muscle to the liver for protein production. Fatty liver does not occur, and serum albumin levels tend to be normal, with no peripheral edema. Often patients fall between these two extremes of nutritional states, but there are examples of kwashiorkor and marasmus in Western clinical practice. Anorexia nervosa is a classic example of marasmus. Marked muscle wasting and loss of subcutaneous tissue (adipose tissue) occur with normal-sized nonfatty livers and no peripheral edema. In contrast, the intensive care unit patient who has received intravenous dextrose (glucose) without amino acids for a prolonged period will often show a fatty liver and marked hypoalbuminemia and edema. Other changes in the liver that may occur in nutritional disorders are listed in Table 3.

Table 3. Effects of specific nutritional disorders on the liver

Nutritional disorders	Effects on the liver
➤ Common conditions	
o Alcoholism	− Steatosis, alcoholic hepatitis and cirrhosis
o Obesity	− Steatosis, steatohepatitis and cholelithiasis
o Uncontrolled diabetes	− Glycogenosis, steatosis and steatohepatitis
o Protein deficiency	− Pigment stones
o Kwashiorkor	− Steatosis and decreased protein synthesis
o Fasting	− Mild unconjugated hyperbilirubinemia, especially in Gilbert's syndrome
➤ Uncommon conditions	
o Jejunoileal bypass	− Steatosis and steatohepatitis
o Gross dietary iron excess	− Bantu siderosis/hemochromatosis
o Senecio alkaloids	− Veno-occlusive disease
o Dietary aflatoxins	− Hepatocellular carcinoma (?)
o Chronic arsenic ingestion	− Noncirrhotic portal hypertension, angiosarcoma and hepatocellular carcinoma
o Hypervitaminosis A	− Hepatic fibrosis and cirrhosis

Clinical vitamin deficiencies are listed in Table 4. Except for cheilosis and glossitis, which are seen with multiple vitamin B deficiencies, physical findings of vitamin deficiencies are seldom observed in protein-calorie malnourished patients in developed countries. Trace elements are elements that are required in small quantities (milligram amounts or less) for normal growth and/or function. Essential trace elements for humans include iron, iodine, zinc, chromium, copper, selenium, cobalt (as vitamin B12), molybdenum, manganese and possibly vanadium. Except for iron deficiency due to blood loss and/or poor intake, deficiency states of trace elements are rare in subjects with some oral intake, since only minute amounts are required.

4. Effects of Malnutrition on the Gastrointestinal Tract and Pancreas

Protein-energy malnutrition may produce major structural and functional changes in the gastrointestinal tract and pancreas, which, in turn, may aggravate the underlying poor nutritional condition. In severe protein-energy malnutrition, for example, acinar cell atrophy occurs and exocrine cells have decreased numbers of zymogen granules. Pancreatic secretion may be reduced following stimulation with cholecystokinin and/or secretin. With malnutrition, the activities of enzymes contained in pancreatic juice (i.e., trypsin, chymotrypsin, lipase and amylase) are reduced. With reversal of malnutrition these can return to normal levels, but this may require several weeks.

In addition to pancreatic exocrine changes, the entire wall and mucosal lining of the stomach and intestine may be reduced in thickness. Microscopically, marked changes may develop, including severe "flattening" of the small intestinal mucosa, similar to celiac disease. In contrast to celiac disease, however, reduced numbers of crypt mitoses are seen. Changes may be present throughout the small intestine in an irregular patchy distribution, although the jejunum appears to be most severely affected. Some brush-border enzymes (e.g., disaccharidases) may be reduced; as a result, malabsorption of a variety of substances (e.g., lactose) may be observed. Altered uptake of glucose and D-xylose has also been reported, and steatorrhea may be present with impaired absorption of fat and some fat-soluble vitamins. In addition, there may be increased protein loss from the gut, leading to increased fecal nitrogen loss. Finally, specific nutrients may be deficient and cause alterations in certain tissues. In particular, folic acid and vitamin B12 deficiencies may lead to subtotal villous atrophy in association with crypt hypoplasia (Table 4).

Table 4. Effects of depletion of specific nutrients on the intestine

Nutrient	Effects
➤ Protein-energy malnutrition (e.g., especially, kwashiorkor)	o Total or subtotal villous atrophy and crypt hypoplasia
➤ Folic acid deficiency	o Total or subtotal villous atrophy and crypt hypoplasia; macrocytic and/or "megaloblastic" enterocytes
➤ Vitamin B12 deficiency	o Total or subtotal villous atrophy and crypt hypoplasia; macrocytic and/or "megaloblastic" enterocytes
➤ Vitamin E deficiency	o (?) Small intestinal ceroidosis (i.e., "brown bowel syndrome")
➤ Vitamin A deficiency	o Reduced numbers of intestinal goblet cells

Restitution of small bowel mucosa occurs after renutrition. There is growing evidence that mucosal atrophy occurs during total parenteral nutrition with associated increased intestinal permeability, especially in stressed metabolic states, and that atrophy is absent or minimal in patients fed enterally. Therefore, whenever possible, intestinal (i.e., enteral) feeding is preferred to parenteral feeding. When refeeding occurs after a period of malnutrition, however, it should be appreciated that gut function may be impaired, with resultant malabsorption and diarrhea, and that total refeeding via the gut may not initially be achieved. In this circumstance, partial enteral refeeding with parenteral supplementation is usually given, provided there are no contraindications to enteral feeding (e.g., bowel obstruction).

There is evidence that the colonic mucosa uses short-chain fatty acids (especially butyrate) as an energy source. In patients who undergo a colostomy, the bowel that is left distally does not have a fecal stream. The mucosa of this bowel may develop inflammation, called "diversion colitis." Some improvement in the colitis has been reported with administration of short-chain fatty acid enemas or with irrigation of fiber. A major source of the short-chain fatty acids in the colon is fermented dietary fiber, and thus fiber may be considered a "nutrient."

5. Dietary Therapy in Gastrointestinal Disease
5.1. General Principles

A number of specific diets are useful in different gastrointestinal disorders. These may involve diet restriction or supplementation, or alternatively, a change in the consistency or content of specific nutrients. In patients with steatorrhea, for example, luminal fatty acids are present and involved in the pathogenesis of diarrhea. In these patients, reduction in diarrhea can be accomplished, in part, by a reduction in the oral intake of triglycerides; a low-fat diet may be beneficial. In some patients with steatorrhea, supplementation with medium-chain triglycerides may be useful because these are hydrolyzed more rapidly by pancreatic enzymes, do not require bile acid micelles for absorption, and are primarily directed to the portal rather than the lymphatic circulation. Because medium-chain triglycerides undergo ω-oxidation to metabolically nonutilizable dicarboxylic acids, the effective caloric content of medium-chain triglycerides is less than expected. Medium-chain triglycerides in a daily dose of 60 mL will provide approximately 460 calories. Low-fat dietary supplements may be provided in the form of a number of commercially available products prepared as complete nutritional supplements. Fat-soluble vitamins can be replaced using oral water-miscible formulations, if steatorrhea is present. For vitamin K, a water-soluble form is available. Fat-soluble vitamins require bile acid micelles for absorption; thus, if steatorrhea is due to bile acid depletion (as might occur in the short bowel syndrome following surgical resection for extensive Crohn disease), increased amounts of vitamins may be required.

Bloating and cramping pain may follow ingestion of lactose-containing foods. This may be due to lactase deficiency (e.g., small bowel disease, "ethnic" lactase deficiency). Dietary lactose restriction may be indicated in patients if there is a history of lactose intolerance or a positive lactose tolerance test (i.e., rise in blood sugar less than 20 mg/dL [1.1 mmol] after 50 g of lactose) accompanied by characteristic symptoms. An alternative test is the lactose breath hydrogen test, in which 2 g/kg (up to 25 g) of lactose is ingested and breath hydrogen is measured. An increase in breath hydrogen of greater than 20 ppm is considered diagnostic of lactose intolerance.

Lactose may be found in milk, including buttermilk, even if it has been naturally fermented. Commercial yogurt should also be avoided, since this often has milk or cream added

after fermentation to avoid the sour taste produced by fermenting lactose. Ice cream and sherbets have high lactose concentrations and should be avoided. Cheese or desserts made from milk or milk chocolate as well as sauces or stuffings made from milk, cream or cheese should also be avoided. Calcium supplements may be necessary with dairy product restriction, particularly in postmenopausal women. Liquid dairy products may be used to a limited extent by patients who have lactose intolerance; in these patients, an enzyme preparation (prepared from yeast or bacteria) added to milk at 4°C (15 drops/L) can hydrolyze up to 99% of the lactose in 24 hours. Nonliquid dairy products cannot be treated with enzyme preparations, although lactase tablets may be chewed prior to eating solid food.

5.2. Celiac Disease

Celiac disease, also known as gluten-sensitive enteropathy or celiac sprue, is a malabsorption disorder resulting from ingestion of proteins derived from certain cereal grains of the grass family, Gramineae: wheat, rye, barley Although oats is not directly related, this grain is believed to be often contaminated with others so that it is usually restricted, although oats certified to be gluten-free are available. It is believed that the alcohol-soluble gliadin fraction of wheat gluten or similar alcohol-soluble proteins from the other grains (termed *prolamins*) cause the intestinal damage. Consequently, absolute restriction is required for life. Table 5 provides some dietary guidelines for celiac disease patients. Gluten, however, is a particularly ubiquitous substance and can be found in coffee, catsup, dip, frozen TV dinners, ice cream and even in the capsules of medications! Although wheat, rye, barley and possibly oats are important, corn and rice do not appear to activate celiac disease. Data on other grains are not as clear. Buckwheat is not derived from the grass family and is usually permitted. Millet and sorghum are often allowed, but have not been thoroughly evaluated. Triticale, a hybrid of wheat and rye, should be avoided. Rye whiskey, Scotch whiskey and other cereal-derived alcohols can be consumed, since gluten is not present in distilled spirits. Similarly, brandy and wine made from fruit pose no difficulties. Beer and ale are produced from barley; it is not entirely clear if they can activate disease and would best be avoided. Malt made from barley should be avoided, as well as hydrolyzed vegetable proteins used as flavor enhancers in processed foods, since they may be made from soy, wheat and other cereal proteins.

Table 5. Dietary guidelines for celiac disease patients

➤ Foods to avoid
  o Wheat, rye, barley, oat products Triticale (wheat–rye hybrid) Millet and sorghum Malt and hydrolyzed vegetable protein

➤ Acceptable foods
  o Corn, rice, buckwheat products
  o Wine and distilled alcoholic beverages
  o Fruits and vegetables
  o Meat
  o Nuts
  o Dairy products (unless lactose-intolerant)

For both symptomatic and asymptomatic patients with celiac disease, a lifelong gluten-free diet is recommended. Multivitamin supplements are frequently required and specific vitamin,

mineral and trace element deficiencies should be corrected. Iron and folate supplementation may be needed and poor absorption of oral iron may sometimes necessitate parenteral administration. Supplements of calcium and vitamin D may be required to prevent mobilization of skeletal calcium, and in some patients magnesium may be needed.

5.3. Inflammatory Bowel Disease

Malnutrition in patients with inflammatory bowel disease, especially Crohn disease, is a frequent problem. Weight loss may be seen in over 65% of patients and growth retardation may be observed in up to 40% of children. As shown in Table 6, there are multiple causes for malnutrition, especially in patients with Crohn disease with small bowel involvement. The goal of nutritional management is to ensure adequate nutrient intake with modifications that reduce symptoms. Although only limited studies are available, evidence suggests that energy expenditure in quiescent Crohn disease and ulcerative colitis is no greater than one would predict for a healthy individual. If the disease is quite active, or is accompanied by fever or sepsis, resting energy expenditure increases. Interestingly, patients, even with quiescent Crohn disease, have evidence of increased fat oxidation at rest, similar to findings in starved individuals. There may be increased caloric as well as nutrient requirements, particularly if gastrointestinal losses are substantial and malabsorption is significant. Attention should also be placed on micronutrient deficiencies in these patients, particularly if concomitant malabsorption is present. For example, patients with significant ileal disease or resection require regularly administered parenteral vitamin B12.

Table 6. Malnutrition in inflammatory bowel disease

➢ Reduced oral intake
  o Disease-induced (e.g., postprandial abdominal pain and diarrhea, sitophobia, anorexia, nausea and vomiting)
  o Iatrogenic (e.g., restrictive diets, "fad" diets)

➢ Malabsorption
  o Reduced absorptive surface (e.g., shortened small intestine due to prior resection, diseased segments)
  o Bacterial overgrowth (e.g., associated with strictures and bypassed loops, stasis)
  o Bile salt deficiency after ileal resection (e.g., impaired micelle formation and steatorrhea) Lactase deficiency (e.g., associated with small bowel disease)
  o Drug-induced malabsorption
➢ Increased nutrient loss
  o Protein-losing enteropathy
  o Diarrhea with losses of electrolytes, minerals and trace elements(e.g., potassium, zinc)
  o Gastrointestinal blood loss (e.g., iron loss)
➢ Drug-induced malabsorption
  o Cholestyramine (e.g., bile acids; fat; fat-soluble vitamins, including vitamins D and K)
  o Sulfasalazine (e.g., folic deficiency associated with reduced absorption and increased
  o requirement related to hemolysis)
  o Steroids (e.g., calcium absorption and mobilization)
➢ Increased requirements
  o Chronic inflammatory disease, fever, superimposed infection

Lactose intolerance is no more common in patients with ulcerative colitis than in healthy individuals. Furthermore, lactose intolerance is also probably no more common in patients with Crohn disease. Owing to the problems with malnutrition in Crohn disease, a lactose-restricted diet should not be recommended unless there is clear-cut improvement in diarrhea with lactose restriction.

Specific drugs may also alter nutrient absorption. Cholestyramine is the classic example of an agent that interferes with nutrient (especially cations such as zinc) and drug absorption.

6. Dietary Therapy in Liver Disease

Two important manifestations of chronic liver disease, ascites and portosystemic encephalopathy, have dietary modification as a cornerstone of treatment. The prime dietary objective in the treatment of ascites is sodium restriction. Severe dietary sodium restrictions are no longer recommended since such restrictions will likely promote malnutrition. Restricting dietary sodium to 80 to 120 mmol per day is felt to be appropriate.

Patients with advanced liver disease, including cirrhosis, have a high prevalence of protein-calorie malnutrition which adversely affects the underlying liver disease and results in poor clinical outcome. These patients should take a diet high in protein (1.2 – 1.5 g/kg) and calories (35 – 40 kcal/kg). Restricting protein intake in patients with portosystemic encephalopathy has not been shown to be beneficial in several randomized trials and is therefore not generally recommended. Vegetable protein may be less ammoniagenic that meat, postulated to be due to a number of factors. Factors cited include a vegetarian diet increased dietary fiber in the vegetarian diet leading to increased elimination of nitrogen in the gut and increased levels of plasma arginine and citrulline leading to increased ammonia removal via the Krebs-Henseleit cycle. Patients with portosystemic encephalopathy have increased levels of aromatic amino acids and decreased levels of branched chain amino acids (BCAA). However, the efficacy of BCAA-enriched formulas in treating portosystemic encephalopathy remains controversial due to conflicting trial results and cost.

Cholestatic liver diseases, including primary biliary cirrhosis (PBC), secondary biliary cirrhosis, sclerosing cholangitis and biliary atresia, may be accompanied by malabsorption of fat-soluble vitamins. Vitamin K deficiency can be easily confirmed with the demonstration of a prolonged INR that corrects with administration of parenteral vitamin K. Assays for vitamins D, A and E may also be performed. If confirmatory tests are not available and if there are strong clinical grounds for suspecting a deficiency state, appropriate replacement therapy should be initiated. Table 7 lists a number of hereditary liver diseases for which appropriate therapy includes specific dietary interventions.

Table 7. Diet therapy for hereditary liver diseases

Disorder	Dietary intervention
o Tyrosinemia	− Low-phenylalanine diet
o Hereditary fructose intolerance	− Low-fructose, low-sucrose diet
o Galactosemia	− Galactose-free diet
o Glycogen storage disease	− Continuous glucose feeding
o Cerebrotendinous	− Deoxycholic acid supplementation

		xanthomatosis
o Wilson's disease	−	Low-copper diet, zinc supplementation (together with chelating agent)
o Hemochromatosis	−	Avoidance of excess dietary iron, selection of foods containing phytates or tannins to reduce iron absorption (together with appropriate phlebotomy treatment)
o Cystic fibrosis	−	Low-fat diet, pancreatic enzyme supplements, fat-soluble
	−	vitamin supplements

7. Nutrition Intervention

7.1. Introduction

The decision to intervene nutritionally is based on a number of disparate factors, including the current nutritional status of the patient (well-nourished versus malnourished), the duration of the time the patient will be expected to be unable to eat, the underlying medical condition and the prognosis for recovery. Once the decision to intervene has been made, the next decision is the method of intervention: oral, enteral or parenteral.

7.2. Nutritional Assessment

Malnutrition can affect patient morbidity and mortality. It is thus important to detect malnourished patients and improve their nutritional status by providing nutritional support. There are several methods to assess nutritional status; the best method would be the one that predicts clinical outcome. In particular, the best method would predict nutrition-associated complications that increase the risk of morbidity and mortality in the absence of nutritional intervention.

However, since it is often difficult to dissect out the effects of malnutrition from the effects of disease, nutritional assessment cannot rely on a single parameter or simple model. Furthermore, disease can affect several parameters used for nutritional assessment independently of nutritional status.

7.2.1 Methods of Assessing Nutritional Status (Table 8)

7.2.1.1. Body composition

Several methods can be used to measure various body compartments and most are used within a research protocol. The ones most frequently used clinically are based on a two compartment model: body fat and lean body mass (muscle, bones). This can be assessed, for example, by anthropometry, where triceps and subscapular skinfold thicknesses provide an index of body fat, and mid-arm circumference provides a measure of muscle mass. This method is mostly used in population studies and is less reliable in the individual patient because of inter- and intra-observer variability and the effect of hydration status, age and physical activity.

Table 8. Methods of nutritional assessment

➢ Laboratory determinations
  o albumin, pre-albumin, transferrin, retinol-binding protein lymphocyte count, WBC 24-hour urinary urea nitrogen, nitrogen balance creatinine-height index
  o delayed cutaneous hypersensitivity

➢ Anthropometric measurements
  o height, weight, ideal body weight (IBW), usual body weight (UBW), BMI weight as percent IBW or UBW, % weight loss triceps skinfold thickness, mid-arm circumference and others

➢ Techniques to assess body composition
  o bio-impedance imaging: DEXA, CT scan dilution radioisotope methods, whole body counting

➢ Dietary intake

➢ Miscellaneous
  o muscle function
  o indirect calorimetry

7.2.1.2. Body weight and weight loss

This is a simple measure and is compared to an ideal weight for height, usually by calculating body mass index (BMI). BMI is the weight in kilograms divided by height in meters squared. A normal BMI is 18.5 to 25 kg/m^2. An ideal weight should give a BMI in that range. On the other hand, a BMI less than 18.5 suggests undernutrition and it is associated with significant morbidity and mortality.[2] A BMI over 25 but below 30 suggests overweight. When BMI reaches 30 or above, the patient is obese and high BMI is also associated with increased risk of morbidity and mortality.[2] A history of weight loss is also important. Studies have shown that unintentional weight loss of > 10% is a good predictor of adverse clinical outcome.

7.2.1.3. Creatinine-height index (CHI)

The excretion of creatinine in the urine is related to muscle mass. Normalized for height, the 24-hour creatinine excretion is an index of muscle mass and can be compared to published tables. However, in a hospital environment, this is not used because of frequent underlying renal disease and use of diuretics.

7.2.1.4. Plasma proteins

Albumin is one of the most studied proteins and several studies have demonstrated that low serum albumin concentration correlates with an increased incidence of medical complications and mortality.[1] However, serum albumin may be inappropriate as a measure of nutritional status because it represents the summation of many events: synthesis, degradation, losses, exchange between intravascular and extra-vascular compartment and volume of distribution. Therefore, hospitalized patients may have lower albumin levels for several reasons: inflammatory disorders

cause a decrease in albumin synthesis, an increase in albumin degradation and trans-capillary losses; gastrointestinal, cardiac and renal diseases as well as wound, burns and peritonitis can cause significant albumin losses and during serious illness, vascular permeability increases dramatically (with loss of albumin into the interstitial space). On the other hand, protein-calorie malnutrition causes a decrease in the rate of albumin synthesis, but a short-term reduction in albumin synthesis will have little impact because of albumin's low turnover rate (half-life: 20 days) and large pool size. Even during chronic malnutrition, plasma albumin concentration is often maintained because of compensatory decrease in albumin degradation and transfer of extravascular albumin to the intravascular compartment. Another plasma protein, prealbumin, is more responsive to nutritional changes because its turnover rate is rapid with a half-life of 2–3 days. However, it is also influenced by underlying diseases such as inflammation, infections, renal and liver failure. Therefore, it is also an unreliable index of nutritional status in patients.

7.2.1.5. Immune competence

As measured by delayed cutaneous hypersensitivity is affected by severe malnutrition. However, other diseases and drugs may also influence the measurements making it a poor predictor of malnutrition in sick patients.

7.2.1.6. Global assessment techniques

Several global assessment techniques exist. A prognostic nutritional index depending largely on albumin and transferrin was shown to provide a quantitative estimate of postoperative complication (Blackburn, 1977). Subjective global assessment (SGA) is a clinical method that has been validated and is able to identify patients who are at risk of developing complications due to malnutrition (Baker 1982). It categorizes the patients as being well nourished (A) or as having moderate or suspected malnutrition (B) or severe malnutrition (C) (Table 10). The use of SGA in evaluating hospitalized patients gives reproducible results and can predict complications in several patient populations such as surgical, dialysis and liver transplant patients.

At present, there is no gold standard for evaluating nutritional status. It is important to recognize the multiple facets of malnutrition to detect the patient at risk of nutrition-related complications. Subjective global assessment combined with selective objective parameters defined above is the best clinical way to detect the patients at risk.

7.3 Nutritional Requirements
7.3.1 Nitrogen Requirements

In a well-nourished adult in steady state, total nitrogen intake will equal nitrogen output in urine, stool, skin and body fluids. This is termed (zero) "nitrogen balance." Nitrogen is assimilated almost exclusively as protein, and, on average, 6.25 g protein is equivalent to 1 g nitrogen. The nitrogen is excreted predominantly as urea in the urine, but stool and skin losses account for about 2–3 g daily. In the steady state, ingestion of more nitrogen will merely result in excretion of more nitrogen in the urine, with the excess protein oxidized in the liver and used as an expensive energy source. In growing children or in malnourished adults, the nutritional goal is a positive nitrogen balance, meaning that body tissue is being formed in excess of what is being broken down (i.e., there is net growth). It is less clear that patients with conditions associated with protein loss, such as nephrotic syndrome and protein-losing enteropathy, benefit from extra protein intake. Indeed, there remains concern with nephrotic syndrome that extra protein may contribute to a fall in glomerular filtration rate (GFR), as has been reported in other renal

conditions.

If energy requirements are met or exceeded, studies have shown that well-nourished adults can maintain nitrogen balance when given as little as 0.6 g/kg protein intake. In order to allow for biologic variability, the standard recommendation for protein intake is 0.75 g/kg. It is important that the protein supplied be of high quality; it should include all essential amino acids and a balanced mix of nonessential amino acids. Malnourished, septic, injured or burned patients will require more protein, in the order of 1.0–2.0 g/kg daily. Pregnant patients should also be given 1.5 g/kg protein daily. It is not clear that patients with conditions associated with protein loss, such as protein-losing enteropathy, benefit from extra protein intake. Indeed, patients with nephrotic syndrome may even benefit from protein restriction, though this is not firmly established.

7.3.2 Energy Requirements

Resting energy requirements in average weight healthy subjects can be accurately predicted with reasonable accuracy by the Harris-Benedict equation:

MALES: Energy (kcal/d) = 66 + (13.75 × W) + (5.00 × H) − (6.78 × A)
FEMALES: Energy (kcal/d) = 655 + (9.56 × W) + (1.85 × H) − (4.68 × A) where W = weight in kg, H = height in cm and A = age in years.

The Harris-Benedict equation may be less accurate in malnourished or obese individuals. Malnourished patients exhibit resting energy requirements about 10% to 20% below predicted. The resting energy requirements of obese patients will also be below predicted since adipose tissue is less metabolically active than other tissues. In overweight patients, it has been proposed that an adjusted weight be used in the Harris-Benedict equation based on actual and ideal body weight, using the following formula:

Adjusted weight = [(actual body wt - ideal wt) × 0.25] + ideal wt.

The Mifflin-St. Joer (also called Mifflin) formula may be a better choice for calculating resting energy expenditure in the obese patient. The formula is as follows:

For males, REE = 10 × weight (kg) + 6.25 × height (cm) - 5 × age (y) + 5
For females, REE = 10 × weight (kg) + 6.25 × height (cm) - 5 × age (y) - 161

Formulas applied to individuals may be inaccurate for a variety of reasons. The population of subjects upon which the formula is based needs to be understood. Race, age, disease state and BMI are several factors which might profoundly affect the REE of an individual, so the formula used must be considered only a guideline in deciding energy requirements.

Basal energy requirements, as predicted by these equations, increase in the presence of fever (13% per °C), sepsis or injury (up to 20–30%), and burns (up to 100%). Modest physical activity usually requires about 30% above basal requirements.

7.4. Types of Nutritional Intervention

The options for refeeding include oral refeeding, tube feeding and total parenteral nutrition. An assessment by a dietitian regarding current food intake and food preferences is essential. It may well be possible by determining food preferences to provide a well-balanced, nutritionally

complete diet. In addition, supplements of high-calorie, high-protein foods such as milkshakes or commercially prepared liquid formula diets may allow for adequate intake. If the patient will not or cannot eat, however, nutritional intervention may be indicated. Examples of patients who will not eat include those with anorexia due to tumor or chemotherapy, and those with anorexia nervosa. Such patients generally have a normal or near-normal nonobstructed bowel, and can be fed enterally. Patients who cannot eat because of severe gastrointestinal illness include those with bowel obstruction or ileus. If nutritional intervention is required in these patients, parenteral (intravenous) nutrition will be necessary.

7.4.1 Enteral Nutrition
7.4.1.1 Methods of delivery

Enteral nutrition generally refers to nutrition provided through a tube that has been inserted into the gastrointestinal tract. Usually the tube is a fine-bore (10 French [3.3 mm] or less) silicone, polyvinylchloride or polyurethane tube placed via the nose into the stomach, duodenum or jejunum. When long-term feeding is required, it is often preferable for cosmetic and comfort reasons to perform a gastrostomy radiologically or endoscopically, the latter commonly referred to as a PEG (percutaneous endoscopic gastrostomy). These tubes can be placed through the pylorus to feed into the jejunum with only local anesthetic and mild sedation. Despite convincing evidence of efficacy of post-pyloric placement of tubes in reducing pulmonary aspiration, the tube is usually placed in the jejunum if aspiration is a concern.

7.4.1.2 Enteral formulas

A multitude of commercial enteral formulas are available for infusion. The formulas have been traditionally divided into polymeric, oligomeric, monomeric, modular and disease-specific formulas. Polymeric formulas (also called defined formula diets) provide nitrogen as whole protein, often casein, egg white solids or soy protein. Carbohydrate is often provided as corn syrup, maltodextrins or glucose oligosaccharides, with sucrose added for sweetness in oral formulas. Fat is usually provided as soy oil, although corn oil and safflower oil may be used. Medium-chain triglycerides (MCT oil) are rarely used. Protein may be provided as milk (usually dry or skim), with lactose as a major carbohydrate. These formulas are contraindicated in patients with lactose intolerance.

Specialized polymeric formulas are available for a variety of disease states, including kidney and lung disease as well as diabetes. The efficacy of these products has generally not been well established. Products also vary in caloric density (usually between 1.0 and 2.0 kcal/mL) and protein content. Some contain fiber and others are prepared for oral consumption (generally sweeter with a higher osmolality than those meant primarily for tube feeding).

Oligomeric formulas (also called semi-elemental diets) provide nitrogen as peptides from partially hydrolyzed whole protein. Monomeric formulas (also called elemental diets) provide nitrogen as crystalline amino acids. Carbohydrate tends to be provided as glucose oligosaccharides. Fat is usually present in small quantities, enough to meet the requirement for linoleic acid (an essential fatty acid), which is about 2–4% of total calories. MCT oil is added to some formulas. The oligomeric and monomeric diets were formulated to require minimal digestion by the gastrointestinal tract, with little necessity for bile and pancreatic secretions, and minimal "work" by the enterocyte in terms of brush-border enzyme activity or re-esterification. Hence, these diets have been commercially promoted as ideal for patients with decreased bile output (cholestasis), pancreatic insufficiency and short bowel. However, there is little evidence

that these diets are superior to polymeric diets. Furthermore, since the diet is "predigested," osmolality is high. Finally, the high cost of these diets (often five to 10 times that of polymeric diets) rarely justifies their use.

Most of these formulas provide enough protein, calories, water, electrolytes, minerals, vitamins and trace elements in 2 L/day or less for most "nonstressed" patients. In other words, these diets are "complete." Excess requirements may exist in patients with multiple injuries, major infections or burns.

As with polymeric formulas, specialized amino acid solutions have been made for use in special circumstances – for example, liver disease, renal disease and "stress," such as trauma and sepsis. For liver disease, these solutions are composed mostly or exclusively of branched-chain amino acids, whereas for renal disease the solutions are predominantly essential amino acids. In general, these solutions are expensive and their efficacy is controversial.

There has been considerable interest in "immunonutrition" which refers to formulas which have been enriched with nutrients purported to alter immunity. Such nutrients include amino acids such as arginine and glutamine, fish oil (omega-3 fatty acids), antioxidants and nucleotides. Systematic reviews of immunonutrition have been reported in intensive care and surgical patients but the role of these specialized products remains controversial.

7.4.1.3 Complications

Complications of enteral feeding may be divided into aspiration, mechanical, gastrointestinal and metabolic. In general, enteral feeding is well tolerated, and provided the complications are known, preventive and/or corrective measures may be undertaken to minimize patient risk.

Aspiration of the infused formula, with development of pneumonia, is a potentially lethal complication of tube feeding. Proper positioning of the tube requires radiographic verification. Risk factors for aspiration include patients on a ventilator and those with gastroesophageal reflux, poor or absent gag reflex, and impaired mentation. To minimize aspiration, it is suggested that patients, when possible, be fed with the head of the bed elevated 20–30°. Gastric contents should initially be checked by aspirating the tube every four to six hours and if the residual volume is > 150 mL, the infusion should be temporarily stopped. Unfortunately, the small nasoenteric tubes in current use often collapse when aspirated, so small returns do not guarantee that the stomach is not becoming distended with fluid. Hence, examination for epigastric distention and succussion splash should be done. If there is any concern, an upright (if possible) plain film to assess gastric size may be useful. It has also been suggested that the feeding tube be placed into the small bowel well beyond the pylorus to minimize aspiration in those at risk, though studies have failed to confirm this.

The following mechanical problems in patients with nasoenteric tubes include problems in the upper respiratory tract and esophagitis with development of esophageal ulceration, stenosis and even tracheoesophageal fistula. Upper respiratory problems include pharyngeal irritation, nasal erosions and necrosis, sinusitis and otitis media. These mechanical problems can be largely avoided by the use of soft, small-bore nasoenteric tubes.

Gastrointestinal problems related to nasoenteric feeding are common, occurring in 20–30% of patients. The most frequent complaints are nausea, vomiting, abdominal distention and altered bowel habit. Symptoms may be minimized by feeding at a slow rate with dilute solutions, but these symptoms may be just as common as with full-rate, full-strength solutions. Alternatively, a different enteral solution may be tried. If a lactose-containing solution is being used (generally

not recommended for tube feeding), changing to a lactose-free solution is indicated. For constipation, fiber-containing solutions may be tried, although they are often unhelpful. Fiber, however, is a potential energy source for the colon, as previously discussed, and may therefore be important for maintenance of the colonic mucosa. At the present time, fiber-containing solutions are not routinely used.

Metabolic complications include overhydration, dehydration, hyperglycemia (including hyperosmolar nonketotic coma) and electrolyte disturbances. Electrolyte problems include hyponatremia, hyper- and hypokalemia, hyper- and hypophosphatemia and hypomagnesemia. In healthy, reasonably nourished individuals with normal cardiac, liver and renal function, these problems are not common. It is recommended that appropriate blood tests be done at intervals over the first few weeks to check for these potential problems.

7.4.2 Total Parenteral Nutrition

Total parenteral nutrition (TPN) involves intravenous administration of all known essential nutrients. This form of therapy is as effective as oral or enteral intake in terms of growth and maintaining body nitrogen. Indications include inability to eat for a minimum of seven to 10 days with a nonfunctional gut. Total parenteral nutrition is also used for "bowel rest," especially in Crohn disease, intestinal fistulas and pancreatitis, even if adequate absorption is possible. Several studies suggest, however, that bowel rest is not helpful in Crohn disease. Furthermore, other studies have shown that elemental diets can be used instead of TPN, except when bowel obstruction is present. In general, if the gut is functional, enteral feeding is preferred since it is safer, cheaper and more physiologic.

7.4.2.1 Solutions

Amino acids "Protein" is supplied as synthetic crystalline, L-amino acid solutions; these are commercially available in 5-20% concentrations. Specialized amino acid solutions for liver and kidney disease have been discontinued in many jurisdictions.

Fat The predominant source of fat in parenteral nutrition has been soybean oil, which has a high concentration of linoleic acid, an omega-6 essential fatty acid in humans as a precursor to arachadonic acid. It has been estimated that 2-4% of total calories should be provided to avoid essential fatty acid deficiency. There has been concern that providing fat solely as a soybean emulsion may not be ideal, which has led to the development of alternative sources of oils for parenteral infusion. Both olive oil and fish oil are available commercially in many parts of the world, alone or as part of a mixture. Parenteral lipid emulsions are available mostly as 20% or 30% (weight/volume) concentrations.

Carbohydrate Glucose is the preferred carbohydrate for intravenous use. Glucose is widely available in concentrations from 5–70%. The osmolality of these solutions may be markedly hyperosmolar up to about 2,500 mOsmol/L.

Nonprotein energy source Once the initial 100 g of glucose is provided for use in the brain, renal medulla and red blood cells, glucose and fat are equally effective in preserving body nitrogen after an equilibration period of four to five days. Glucose is very inexpensive as an energy source, but requires insulin for uptake into cells, and hyperglycemia can be a problem when large amounts of glucose are utilized. The high osmolality of glucose solutions means that only dilute solutions can be used in peripheral veins, and if glucose is used as a major energy source, a large central vein is necessary to prevent thrombosis. Furthermore, glucose has a respiratory quotient (R.Q. = CO_2 produced/O_2 consumed) of 1.0, meaning that large amounts of

carbon dioxide may be produced. Finally, glucose infusion leads to catecholamine release and increased metabolic rate, further increasing carbon dioxide production. These changes may be deleterious for patients being weaned from ventilators, or with borderline respiratory function.

Lipid solutions offer the benefit of being iso-osmolar, containing essential fatty acids and having a lower respiratory quotient of 0.7, with less carbon dioxide production. Drawbacks include somewhat higher cost compared to glucose, and poor tolerance in patients with hyperlipidemia.

Combined solutions

While parenteral nutrition solutions are available as separate amino acid, lipid and glucose components, there has been increased use of solutions which have been mixed commercially ("premixed"), either as a "2 in 1" (amino acid/glucose with lipid provided separately) or as a "3 in 1" (amino acid/glucose/lipid) mixture.

7.4.2.2 Routes of delivery

Central   The most flexible way to deliver total parenteral nutrition is through a large central vein, usually the superior vena cava, usually via the subclavian vein or a peripheral vein, the latter by using a peripherally inserted peripheral catheter (PICC). With the large flow through the superior vena cava, solution osmolality is not of great concern, and thrombosis of this vessel is uncommon.

Peripheral The high osmolality of parenteral nutrition solutions and the widespread availability limit the indications for parenteral nutrition provided by a peripheral (non-central) catheter. However, parenteral nutrition may be appropriate when central venous catheterization is not possible, advisable or feasible and the duration of parenteral nutrition is expected to be short term (preferably not longer than 2 weeks). Since the parenteral nutrition solutions must be of relatively low osmolality ($\leq$ 900 mosm/L), the patient must be able to tolerate large (> 2 L) volumes. Midline (7.5-20 cm) 22 or 23 gauge catheters made from polyurethane or silicone may last up to 2 weeks and are preferred over short (< 7.5 cm) catheters. There are commercially available premixed solutions available for peripheral parenteral nutrition.

7.4.2.3 Complications

Complications of total parenteral nutrition may be divided into local and systemic. Local problems relate to the catheter site, and in the case of central lines involve all the complications of central catheters, including inadvertent arterial catheterization with bleeding, pneumothorax, hemothorax and inadvertent infusion of solutions into the pleural cavity. Air embolism may occur at the time of insertion or any time thereafter with a central line. Catheter embolization may occur, and as mentioned, thrombosis has been reported, particularly with the use of stiff catheters. It is essential that catheter placement be done by persons with considerable experience to minimize these complications.

Systemic complications include sepsis, metabolic problems and bone disease. Bacteremia or fungemia occurs in 3–7% of patients given total parenteral nutrition, and this appears to arise predominantly from the hub where the catheter joins the intravenous tubing. Catheters are always inserted in a strictly aseptic manner, with personnel fully gowned and gloved. Metabolic problems include hyperglycemia, which can be treated by reducing the amount of glucose given in the solutions, hypertriglyceridemia when excess calories and/or excess lipid are given, and alterations in electrolytes. In particular, total parenteral nutrition causes anabolism with increased

intracellular water, so that potassium and phosphate are driven into cells, leading to possible hypokalemia and hypophosphatemia. These complications are very uncommon if adequate amounts of these electrolytes are provided and careful monitoring is performed (daily values for at least 3 days). Liver disease remains a frustrating complication of total parenteral nutrition, but in most cases the changes are restricted to enzyme elevations. In general, mild elevations in AST and alkaline phosphatase occur in the second week, with occasional elevations in bilirubin occurring later. Liver biopsy may show mild cholestasis. Some of these changes may be due to overfeeding or by providing lipid in excess of 1 g/kg; this can be treated by reducing total calories and by ensuring excess lipid is not given. Providing a lipid solution high in omega-3 fatty acids (fish oil) may result in improvement in liver tests, with the best data in the pediatric patient. Rarely, long-term TPN (extending over years) may result in cirrhosis without a well-defined cause.

7.4.3 Home Enteral and Parenteral Nutrition

7.4.3.1 Home enteral nutrition

Enteral nutrition may be provided on a long-term basis at home using any of the standard enteral formulas. While highly motivated individuals may do this using nasogastric tubes placed nightly with nocturnal feedings, most patients will need a gastrostomy or jejunostomy tube for long-term feeding. Intermittent bloodwork and physician follow-up visits, similar to home parenteral nutrition, will need to be done to ensure that the formula is appropriate and that the nutritional goals are being met. The patient or caregiver must be adequately versed in the management of the gastrostomy and jejunostomy tubes as well as in the potential complications of enteral feeding using such tubes. Intermittent replacement of these tubes is generally on an as-needed basis although some nutrition programs provide replacement on a predefined timetable, for example every 12 to 18 months.

7.4.3.2   Home parenteral nutrition

Home parenteral nutrition is used in patients who require long-term parenteral nutrition but who do not need hospital admission for any other medical reason. These patients have gut failure due to short bowel syndrome (e.g., Crohn disease, ischemic bowel disease), severe motility disturbances (scleroderma, idiopathic pseudo-obstruction), hyperemesis gravidarum and other miscellaneous problems.

Home parenteral nutrition patients and/or their caregivers need to undergo appropriate training in aseptic techniques as well as training in management of catheter and pump care. This training may be done in a hospital setting or in an outpatient setting depending on the underlying condition of the patient. Regular bloodwork and follow-up visits with the physician, home care nurse and dietitian are essential.

Long-term complications of home parenteral nutrition include the usual complications of parenteral nutrition. However, line sepsis, venous thrombosis and liver disease represent profound challenges in the long-term setting. Metabolic bone disease is also common in patients receiving home parenteral nutrition, but is likely due to the underlying conditions which require home parenteral nutrition (e.g., Crohn disease with previous corticosteroid use) rather than due to the parenteral nutrition itself.

7.5. Nutrition Support in Specific Conditions

7.5.1 The Malnourished Patient

The malnourished patient represents a special challenge in nutrition. Malnourished patients have energy requirements which are 10% to 20% below predicted by the Harris-Benedict equation, as discussed above. Furthermore, such patients are at particular risk for "refeeding syndrome," consisting of a variety of problems occurring when nutrition is initiated. Fluid retention with marked edema and even congestive heart failure may occur. As the intracellular compartment is regenerated with refeeding, there may be shifts of extracellular substances into the cell including phosphorous, potassium and magnesium. These shifts are facilitated by insulin which is released in response to glucose given as part of the nutrition. It is very important to provide adequate amounts of phosphorous, potassium and magnesium. Other problems include glucose intolerance and thiamine deficiency.

With the above problems in mind, the malnourished patient who is being re-fed requires careful clinical monitoring of fluid status and daily measurement of serum phosphorous, potassium, magnesium and glucose until normal, stable levels are obtained. Vitamins, especially thiamine, should be administered at the onset of nutritional repletion and continued for several days.

7.5.2 Crohn disease

Crohn disease represents a special situation for nutrition due to potential problems with strictures, short bowel and sepsis. Parenteral nutrition plays a role as adjunct therapy in Crohn's patients who are obstructed or have short bowel syndrome.There is clearly a role for enteral nutrition in the pediatric population, where this modality provides for linear growth in growth-retarded patients. It should be noted that monomeric (elemental) diets have not been shown to be more effective than polymeric diets when these formulas have been compared.

7.4.4 Pancreatitis

Pancreatitis offers a unique challenge in nutrition. First, infusion of nutrients into the duodenum stimulates pancreatic secretion, which may be theoretically harmful in patients with pancreatitis. Second, patients with pancreatitis frequently have vomiting and ileus as a manifestation of their condition. Finally, the pancreas secretes both exocrine and endocrine products important in nutrition, namely pancreatic enzymes and insulin. Despite these considerations, the preferred method of providing nutrition in acute pancreatitis is elemental jejunal feeding which has been found to be safer than parenteral nutrition with fewer septic complications. Uncommonly, parenteral nutrition may be necessary if enteral feeding is not tolerated.

Suggested Reading and References

COMMON SYMPTOMS AND SIGNS IN GASTROENTEROLOGY

Bates' Guide to Physical Examination and History Taking. Lynn S Bickley. Lippincott Williams and Wilkins.2008

Castell DO, et al. Estimation of liver size by percussion in normal individuals. Annals of Internal Medicine 1969; 70(6):1183-1189.

Grover SA, et al. Does this patient have splenomegaly? *Journal of the American Medical Association* 1993; 270:2218-2221.

Naylor CD. Physical examination of the liver. *Journal of the American Medical Association* 1994; 271:1859-1865.

Sapira JD. The art and science of bedside teaching. In: Sapira JD (ed.), The art and science of bedside diagnosis. Baltimore: Urban & Schwarzenberg, 1990.

Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th edition. Section 2. Approach to patients with symptoms and signs. p 87-318.

Williams JW, et al. Does this patient have ascites? How to divine fluid in the abdomen. *Journal of the American Medical Association* 1992; 267:2645-2648.

ESOGPHAGUS

ESOPHAGUS

➤ *Gastroesophageal reflux disease (GERD)*

Ali RAR, et al. Gastroesophageal reflux disease in pregnancy. *Best Practice & Research Clinical Gastroenterology* 2007;21(5):793-806.

Ang D. Mechanisms of Heartburn. *Nature Clinical Practice Gastroenterology & Hepatology*. 2008;5(7):383-392.

Armstrong D, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults – update 2004. *Canadian Journal of Gastroenterology* 2005; 19:15-35.

Armstrong D. Systematic Review: persistence and severity in gastro-oesophageal reflux disease. *Alimentary Pharmacology and Therapeutics* 2008;28(7):841-853.

Bingbinb Q., et al. Effects of *Helicobacter pylori* eradication on gastroesophageal reflux disease. *Helicobacter* 2011;16:255-265.

Blondeau K, et al. Usefulness of impedance testing in the management of GERD. *The American Journal of Gastroenterology* 2009;104:2664-2666.

Castell D. Medication-induced esophagitis. *UpToDate online journal*. www.uptodate.com.

Dent J. Endoscopic grading of reflux oesophagitis: the past, present, and future. *Best Practice & Research Clinical Gastroenterology* 2008;22(4):585-599.

Donnellan C, et al. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database of Systematic Reviews 2009.*

Epstein D, et al. The REFLUX trial group. Laparoscopic fundoplication compared with medical management for gastro oesophageal reflux disease: cost effectiveness study. *British Medical Journal* 2009;338:b2576.

Fox MR. Oesophageal high resolution manometry: moving from research into clinical practice. *Gut* 2008;57(3):405-423.

Galmiche JP. Functional Esophageal Disorders. *Gastroenterology* 2006;130:1459-1465.

Galmiche JP. Respiratory manifestation of gastroesophageal reflux disease. *Alimentary Pharmacology and Therapeutics* 2008;27(6):449-464.

Heading RC. Complete Remission in GERD: Dream or Reality? *Journal of Clinical Gastroenterology* 2007;41:S198-S203.

Hemmink GJM, et al. Aerophagia: Excessive air swallowing demonstrated by esophageal impedance monitoring. *Clinical Gastroenterology and Hepatology* 2009;7:1127-1129.

Hershcovici T and Fass R. An algorithm for diagnosis and treatment of refractory GERD. *Best Practice & Research, Clinical Gastroenterology*. 2010;24(6):923-36.

Hirano I. Review article: modern technology in the diagnosis of gastro-oesophageal reflux disease – Bilitec, intraluminal impedance and Bravo capsule pH monitoring. *Alimentary Pharmacology and Therapeutics* 2006; 23(Supp 1):12-24.

James C. Slaughter, et al. Caution About Overinterpretation of Symptom Indexes in Reflux Monitoring for Refractory Gastroesophageal Reflux Disease. *Clinical Gastroenterology and Hepatology*. 2011;9:868-874.

Kahrilas PJ. American Gastroenterological Association Institute Technical Review on the Management of Gastroesophageal Reflux Disease. *Gastroenterology* 2008; 135:1392-1413.

Kahrilas PJ. American Gastroenterological Association Medical Position statement on the management of Gastroesophageal Reflux Disease. *Gastroenterology* 2008;135:1383-1391.

Kaji M, et al. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. *Journal of Gastroenterology and Hepatology.* 2010;25(6):1151-6.

Lacy BE, et al. The diagnosis of gastroesophageal reflux disease. *The American Journal of Medicine*. 2010;123(7):583-592.

Larghi A, et al. High-resolution narrow band imaging endoscopy. Gut 2008;57(7):976-986.

Lauren B. Gerson, et al. Insights Into Gastroesophageal Reflux Disease–Associated Dyspeptic Symptoms. *Clinical Gastroenterology and Hepatology.* 2011; 9:824-833.

Lee SY, et al. Prevalence and risk factors for overlaps between gastroesophageal reflux disease, dyspepsia, and irritable bowel syndrome: a population-based study. *Digestion.* 2009;79(3):196-201.

Lundell L, et al. and the Nordic Gerd Study Group. Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clinical Gastroenterology and Hepatology* 2009;7:1292-1298.

Mahieu HF. The Laryngological manifestations of reflux disease: why the skepticism? *Alimentary Pharmacology and Therapeutics* 2007;26(Suppl 2):17-24.

Moayyedi P, et al. Medical treatments in the short term management of reflux oesophagitis. *Cochrane Database of Systematic Reviews 2009*

Monnikes H. Global Clinical Symptom Spectrum in Gastroesophageal Reflux Disease. *Journal of Clinical Gastroenterology* 2007;41:S168-S174.

Murray JA. Gastroesophageal reflux disease. *Mayo Clinic Gastroenterology and Hepatology Board Review Third Edition 2008:* 3-20.

Noh YW, et al. Overlap of Erosive and Non-erosive Reflux Diseases With Functional Gastrointestinal Disorders According to Rome III Criteria. *Journal of Neurogastroenterology and Motility.* 2010;16(2):148-56.

Omari TI, et al. A novel method for the nonradiological assessment of ineffective swallowing. *The American Journal of Gastroenterology.* 2011;106(10):1796-802.

Oudkerk PM. Gastro-oesophageal reflux disease application of the concept of complete remission. *Alimentary Pharmacology and Therapeutics* 2007;26(Suppl 2):13-16

Pace F. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Alimentary Pharmacology and Therapeutics* 2007;26(2):195-204

Pandolfino JE, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008;135(5):1526-1533

Patti M. Gastroesophageal Reflux Diseases. Emedicine Online Journal. www.emedicine.com

Pritchett JM, et al. Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. *Clinical Gastroenterology and Hepatology* 2009;7:743-748

Richter JE. Gastroesophageal Reflux Disease. *Best Practice and Research Clinical Gastroenterology* 2007;21(4):609-631.

Schwartz MP. The endoscopic treatment of gastroesophageal reflux disease. *Alimentary Pharmacology and Therapeutics* 2007;26(Suppl 2):1-6.

Siersema, PD. Treatment options for esophageal strictures. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(3):142-152.
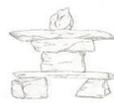
Sifrim, D. et al. Utility of non-endoscopic investigations in the practical management of oesophageal disorders. *Best Practice and Research Clinical Gastroenterology* 2009; 23: 369-386.

Slaughter JC, et al. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. *Clinical Gastroenterology and Hepatology.* 2011;9(10):868-74.

Spechler SJ. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *Journal of the American Medical Association* 2001; 285(28):2331-2338.

Thomson ABR. Update 2008: The Esophagus. *Clincal Medicine Gastroenterology* 2008;1:11-20

Vaezi MF. GERD: What to do when PPIs don't help. *2009 ACG Annual Postgraduate Course*: 6-7.

Vaezi MF. Sore Throat and a Red hypopharynx: Is it Reflux? *Clinical Gastroenteroogyl and Hepatology* 2007;5:1379-1382

Vakil N, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *The American Journal of Gastroenterology* 2006;101(8):1900-1920

Vakil N. Dyspepsia and GERD: breaking the rules. *The American Journal of Gastroenterology* 2005;100(7):1489-1490

van Malenstein H. Esophageal dilated Intercellular spaces (DIS) and nonerosive reflux disease. *The American Journal of Gastroenterology* 2008;103(4):1021-8.

Vasudeva R. Schatzki Ring. http://author.emedicine.com/med/topic2069.htm

Vieth M. Contribution of histology to the diagnosis of reflux disease. *Best Practice & Research Clinical Gastroenterology* 2008;22(4):625-638.

Wikipedia Contributors. Barrett's Esophagus. *Wikipedia, The Free encyclopedia*. July 2, 2009, At 23:26 UTC. Available at http://en.wikipedia.org/wiki/Barrett%27s_esophagus. Accessed August 7, 2009.

Wilcox CM. Esophageal Infections and other human immunodeficiency virus-associated esophageal disorders. Slack Incorporated. http://www.slackbooks.com/excerpts/75112/ 75112. asp

Xaralambos Z. Esophageal Webs and rings. *Emedicine online journal.* www.emedicine.com

Yarandi SS, et al. Overlapping gastroesophageal reflux disease and irritable bowel syndrome: Increased dysfunctional symptoms. *World Journal of Gastroenterology.* 2010; 16(10): 1232–1238.

➢ *Barrett's epithelium*

Ajumobi A, et al. Surveillance in Barrett's esophagus: an audit of practice. *Digestive Diseases and Sciences.* 2010;55(6):1615-21.

American Gastroenterological Association et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology.* 2011;140:1084-1091.

Ann M. Chen, and Pankaj J. Pasricha, Cryotherapy for Barrett's Esophagus: Who, How, and Why? *Gastrointestinal Endoscopy Clinics.* 2011;21:111-118.

Badreddine RJ, et al. Prevalence and predictors of recurrent neoplasia after ablation of Barrett's esophagus. *Gastrointestinal Endoscopy.* 2010;71(4):697-703.

Barbiere JM, et al. Cost effectiveness of endoscopic screening followed by surveillance for Barrett's esophagus: A review. *Gastroenterology* 2009;137:1869-1876.

Bulsiewicz WJ and Shaheen NJ. The role of radiofrequency ablation in the management of Barrett's esophagus. *Gastrointestinal Endoscopy Clinics of North America.* 2011;21(1):95-109.

Canto MI. Endomicroscopy of Barrett's Esophagus. *Gastroenterology Clinics of North America.* 2010;39(4):759-69.

Chang JT, et al. Gastroesophageal reflux disease, Barrett esophagus, and esophageal adenocarcinoma. *Archives of Internal Medicine* 2004;164:1482-1488.

Chen AM, et al. Cryotherapy for Barrett's esophagus: Who, how, and why? *Gastrointestinal Endoscopy Clinics of North America.* 2011; 21 (1): 111-8.

Cobb MJ, et al. Imaging of subsquamous Barrett's epithelium with ultrahigh-resolution optical coherence tomography: a histologic correlation study. *Gastrointestinal Endoscopy.* 2010;71(2):223-30.

Curvers WL, et al. Endoscopic tri-modal imaging is more effective than standard endoscopy in identifying early-stage neoplasia in Barrett's esophagus. *Gastroenterology.* 2010;139(4):1106-14.

Curvers WL, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *The American Journal of Gastroenterology.* 2010;105(7):1523-30.

de Jonge PJ, et al. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. *Gut.* 2010;59(8):1030-6.

Deprez P.H., et al. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. *Endoscopy* 2010;42:853-858.

Fleischer DE, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy.* 2010;42(10):781-9.

Flejou JF. Histological assesement of oesophageal columnar mucosa. *Best Practice & Research Clinical Gastroenterology* 2008; 22(4):671-686.

Herrero L.A., et al. Autofluorescence and narrow band imaging in Barrett's esophagus. *Gastroenterology Clinics of North America* 2010;39:747-758.

J J Mannath, et al. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Endoscopy.* 2010;42(5):351-9

Johnston MH. Barrett Esophagus and Barrett Ulcer. *eMedicine online journal*; www.emedicine.com

Kusunoki M, et al. The incidence of deep vein thrombosis in Japanese patients undergoing endoscopic submucosal dissection. *Gastrointestinal Endoscopy.* 2011 Oct;74(4):798-804.

Mannath J., et al. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Endoscopy* 2010;42:351-359.

Mendelson J., et al. Dysfunctional transforming growth factor-beta signaling with constitutively active notch signaling in Barrett's esophageal adenocarcinoma. *Cancer* 2011; 117:3691-3702.

Nguyen DM, et al Medication usage and the risk of neoplasia in patients with Barrett's esophagus. . *Clinical Gastroenterology and Hepatology* 2009;7:1299-1304.

Nicholas J. Shaheen, et al. Durability of Epithelial Reversion After Radiofrequency Ablation: Follow-up of the AIM Dysplasia Trial. *Gastroenterology.* 2010;138 Issue 5, Supplement 1:S-16-S-17.

Norman S. Nishioka. Drug, light, and oxygen: A dynamic combination in the clinic. *Gastroenterology.* 1998; 114: 604-606.

Overholt BF, et al. Photodynamic therapy with porfirmer sodium for ablation of high-grade dysplasia in Barrett's esophagus: International, partially blinded randomized phase III trial. *Gastrointestinal Endoscopy* 2005;62(4):488-498.

Paterson WG, et al The lower esophageal sphincter. *Clinical & Investigative Medicine* 2002; 25:47–53.

Paterson WG. Canadian Association of Gastroenterology practice guidelines: management of noncardiac chest pain. *Canadian Journal of Gastroenterology* 1998; 12:401-407.

Paterson WG. Extraesophageal manifestations of reflux disease: myths and reality. *Chest surgery clinics of North America* 2001; 11:523-538.

Pauw, R. E., et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. *Clinical Gastroenterology and Hepatology.* 2010;8:233-29.

Pech O, Ell C. Resecting or burning: What should we do with the remaining Barrett's epithelium after successful ER of neoplasia? *The American Journal of Gastroenterology* 2009;104:2693-2694.

Pech O., et al. Comparison Between Endoscopic and Surgical Resection of Mucosal Esophageal Adenocarcinoma in Barrett's Esophagus At Two High-Volume Centers. *Annals of Surgery.* 2011 ; 254:67–72.

Playford RJ. Barrett's oesophagus guidelines for the diagnosis and management of New British Society of Gastroenterology (BSG). *Gut* 2006; 55:442-449.

Pouw RE, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. *Clinical Gastroenterology and Hepatology.* 2010;8(1):23-9.

Pouw RE, et al. Stepwise radical endoscopic resection for eradication of Barrett's oesophagus with early neoplasia in a cohort of 169 patients. *Gut.* 2010;59(9):1169-77.

Prasad GA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. *Gastroenterology.* 2009;137(3):815-23.

Repaka, A. and Chak, A. Endoscopic management of Barrett esophagus. *Nature Review Gastroenterology & Hepatology.* 2011;8:582-591.

Sachin Wani, et al. Risk Factors for Progression of Low-Grade Dysplasia in Patients With Barrett's Esophagus. *Gastroenterology* 2011;141:1179-1186.

Shaheen NJ, et al. Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. *The New England Journal of Medicine*. 2009; 360:2277-2288.

Sharma P. A Critical Review of the Diagnosis and Management of Barrett's Esophagus: The AGA Chicago Workshop. *Gastroenterology* 2004;127:310-330.

Sharma P. Are screening and surveillance for Barrett's oesophagus really worthwhile? *Gut* 2005;54:27-32.

Sikkema M, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. *The American Journal of Gastroenterology*. 2011;106(7):1231-8.

Spechler SJ, Barrett's esophagus without dysplasia: wait or ablate? *Digestive Diseases and Sciences.*2011;56:1962-1928.

Spechler SJ. Epidemiology, clinical manifestations and diagnosis of Barrett's Esophagus. *UpToDate online journal*. www.uptodate.com

Spechler SJ. Pathogenesis of Barrett's esophagus and its malignant transformation. *UpToDate online journal*. www.uptodate.com

Sudarshan R Kadri, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. *British Medical Journal*. 2010; 341: c4372.

Thomas T, et al. High-resolution endoscopy and endoscopic ultrasound for evaluation of early neoplasia in Barrett's esophagus. *Surgical Endoscopy.* 2010;24(5):1110-6.

van Vilsteren FG, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. *Gut*. 2011 ;60(6):765-73.

Vassiliou MC, et al. Treatment of ultralong-segment Barrett's using focal and balloon-based radiofrequency ablation. *Surgical Endoscopy*. 2010;24:786-791.

Wallace MB, et al. Preliminary accuracy and interobserver agreement for the detection of intraepithelial neoplasia in Barrett's esophagus with probe-based confocal laser endomicroscopy. *Gastrointestinal Endoscopy*. 2010;72(1):19-24.

Wang KW. Updated guidelines for the diagnosis, surveillance and therapy for Barrett's esophagus. *The American Journal of Gastroenterology* 2008;103:788-7797

Wani S, et al. Endoscopic eradication of Barrett's esophagus. *Gastrointestinal Endoscopy*. 2010;71(1):147-66.

Wani S, et al. Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. *The American Journal of Gastroenterology*. 2009;104:502-513.

Wani S, et al. Greater interobserver agreement by endoscopic mucosal resection than biopsy samples in Barrett's dysplasia. *Clinical Gastroenterology and Hepatology.* 2010;8(9):783-8.

Wani S, et al. Patients with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clinical Gastroenterology and Hepatology.* 2011;9(3):220-7; quiz e26.

➢ *Esophageal motility disorders*

Boeckxstaens GEE. Achalasia. *Best Practice & Research Clinical Gastroenterology* 2007;21(4):595-608.

Bredenoord AJ. Technology Review: Esophageal Impedance monitoring. *The American Journal of Gastroenteroogyl* 2007;102:187-194.

Clouse RE, et al. Esophageal motor and sensory function and motor disorders of the esophagus. Sleisenger & Fordtran's gastrointestinal and liver disease: *Pathophysiology/Diagnosis/Management* 2006:871.

Dickman R. Noncardiac Chest Pain. *Clinical Gastroenterology & Hepatology* 2006;4:558–563.

Fisichella PM. Achalasia. *Emedicine Online Journal*. www.emedicine.com

Fox MR., et al. Oesophageal high-resolution manometry: moving from research into clinical practice. *Gut* 2008;57:405-423.

Galmiche JP, et al. Functional Esophageal Disorders. *Gastroenterology* 2006;130:1459-1465.

Grubel C, et al. Diffuse Esophageal Spasm. *The American Journal of Gastroenterology* 2008;103:450-457.

Gutschow CA and Hölscher AH. Myotomy for esophageal achalasia - laparoscopic versus peroral endoscopic approach. *Endoscopy.* 2010;42(4):318-9.

Hait EJ, et al. Clinical scenario--an 18-year-old with acute dysphagia and meat impaction. *Clinical Gastroenterology and Hepatology* 2009;7:721-724.

Hemmink GJM, et al. Aerophagia: Excessive air swallowing demonstrated by esophageal impedance monitoring. *Clinical Gastroenterology and Hepatology* 2009;7:1127-1129.

Holloway RH. Esophageal Ultrasonography: A new view on esophageal motility. *American Journal of Gastroenterology* 2007;102(1):146-148.

Inoue H, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy.* 2010;42(4):265-71.

Kaye SA. Gastrointestinal manifestations of systemic sclerosis. *UpToDate online journal.* www.uptodate.com

Korsapati H, et al. Reversal of asynchrony between circular and longitudinal muscle contraction in nutcracker esophagus by atropine. *Gastroenterology* 2008;135(3):796-802

Leeuwenburgh I, et al. Long-Term Esophageal Cancer Risk in Patients With Primary Achalasia: A Prospective Study. *The American Journal of Gastroenterology* 2010;105(10):2144-9.

Lehrer JK et al. Evaluation of unexplained chest pain by the gastroenterologist. A continuing dilemma. *Journal of Clinical Gastroenterology* 2004;38(1):5-6.

Levine MS, et al. Barium Esophagography: A study for all seasons. *Clinical Gastroenterology and Hepatology* 2008;6:11-25.

Mielens JD, et al. Automated analysis of pharyngeal pressure data obtained with high-resolution manometry. *Dysphagia.* 2011;26(1):3-12.

Mittal RK, et al. Oesophageal motor functions and its disorders. *Gut* 2004; 53:1536-1542.

Novais P A, et al. 24-h pH monitoring patterns and clinical response after achalasia treatment with pneumatic dilation or laparoscopic Heller myotomy. *Alimentary Pharmacology and Therapeutics* 2010;32(10):1257-1265.

Omari TI, et al. Reproducibility and agreement of pharyngeal automated impedance manometry with videofluoroscopy. *Clinical Gastroenterology and Hepatology.* 2011;9(10):862-7.

Pandolfino JE, et al. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008;135(5):1526-1533.

Pandolfino JE, et al. Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. *The American Journal of Gastroenterology* 2008;103:27-37.

Pandolfino JE, et al. High resolution manometry in clinical practice: utilizing pressure topography to classify oesophageal motility disorders. *Neurogastroenterology & Motility* 2009;21:796-806.

Pandolfino JE, et al. The second American Gastroenterological Association technical review on the clinical use of esophageal manometry. *Gastroenterology* 2005;128:209-229.

Pandolfino JE, et al. Utilizing intraluminal pressure gradients to predict esophageal clearance: a validation study. *American Journal of Gastroenterol*ogy 2008:103(8):1898-1905

Scarpellini E, et al. The effects of itopride on oesophageal motility and lower oesophageal sphincter function in man. *Alimentary Pharmacology and Therapeutics* 2011;33:99-105.

Sifrim D, et al. Non-achalsic motor disorders of the oesophagus. *Best Practice & Research Clinical Gastroenterology* 2007;21(4): 575-593.

Spechler SJ. Clinical manifestations and diagnosis of achalasia. *UptoDate online journal* 2007; www.uptodate.com

Spechler SJ. Pathophysiology and etiology of achalasia. *UptoDate online journal* 2007; www.uptodate.com

Thomson ABR. Esophageal Spasm. *eMedicine online journal* 2011; www.emedicine.com

Thomson ABR. ReQuest® Pain, pH, and Promises. *Journal of Clinical Gastroenterology* 2007;41:S81-S86.

Tutuian R, et al. Review article: oesophageal spasm – diagnosis and management. *Alimentary Pharmacology and Therapeutics*2006; 23:1393–1402.

Vaezi MF. Diagnosis and management of achalasia. *The American Journal of Gastroenterology* 1999;94(12):3406-3417.

Wilcox CM. Esophageal Infections and other human immunodeficiency virus-associated esophageal disorders. Slack Incorporated. http://www.slackbooks.com/excerpts/ 75112/75112.asp

Williams JF, et al. Non- cardiac chest pain: The long term natural history and comparison with gastroesophageal reflux disease. *The American Journal of Gastroenterology* 2009;104(9):2145-52.

Xaralambos Z. Esophageal Webs and rings. *eMedicine online journal.* www.emedicine.com

➢ *Eosinophilic esophagitis (EoE)*

Atkins D, et al. Eosinophilic esophagitis: the newest esophageal inflammatory disease. *Nat Rev Gastroentol Hepatol* 2009;6(5):267-278

Attwood, SEA, et al. Eosinophilic oesophagitis and other non-reflux inflammatory conditions of the oesophagus: Diagnostic imaging and management. *Best Practice & Research Clinical Gastroenterology* 2008;22(4):639-660.

Bischoff SC. Eosinophils and allergic diseases of the gastrointestinal tract. *Best Practice & Research Clinical Gastroenterology* 2008;22(3):455-479.

Bohm M, et al. Treatment of eosinophilic esophagitis: Overview, current limitations and future directions. *The American Journal of Gastroenteroogyl* 2008;103:1-10.

Conus S, et al. General laboratory diagnostics of eosinophilic GI diseases. *Best Practice & Research Clinical Gastroenterology* 2008;22(3):441-453.

Dellon ES, et al Clincal , endoscopic and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clinical Gastroenterology and Hepatology* 2009;7:1305-1313

Furuta GT, et al. First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: A systemic review and consensus recommendation for diagnosis and treatment.*Gastroenterology* 2007;133:1342.

Hait EJ, et al. Clinical scenario--an 18-year-old with acute dysphagia and meat impaction. *Clinical Gastroenterology and Hepatology* 2009;7:721-724.

Helou EF, et al. Three year follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. *The American Journal of Gastroenterology* 2008;103:2194-2199.

Loscher T. Eosinophilia during intestinal infection. *Best Practice & Research Clinical Gastroenterology* 2008;22(3):511-536.

Mueller S. Classification of eosinophilic gastrointestinal diseases. *Best Practice & Research Clinical Gastroenterology* 2008;22(3):427

Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 2009;137:1238-1249

Wikipedia contributors. Eosinophilic Esophagitis. *Wikipedia, the free encyclopedia*. August 8, 2009 at 04 :52 UTC. Available at : http://en.wikipedia.org/wiki/Eosinophilic_esophagitis. Accessed August 16, 2009.

➤ *Dysphagia*

Cook IJ. Diagnostic Evaluation of Dysphagia. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(7):393-403

Cook, I.J., et al. Oropharyngeal dysphagia *2006 AGA Institute Postgraduate Course*:649-659

Fass R. Approach to the patient with dysphagia. *UptoDate online journal* 2007; www.uptodate.com

Guyomard V, et al. Effect of dysphasia and dysphagia on inpatient mortality and hospital length of stay: a database study. *Journal of the American Geriatrics Society.* 2009;57(11):2101-6.

Lembo AJ. Pathogenesis and clinical manifestations of oropharyngeal dysphagia. *UptoDate online journal* 2007; www.uptodate.com

Pauloski BR, et al. Relationship Between Manometric and Videofluoroscopic Measures of Swallow Function in Healthy Adults and Patients Treated for Head and Neck Cancer with Various Modalities. *Dysphagia.* 2009; 24(2): 196–203.

Robson K. Globus sensation. *UptoDate online journal* 2007; www.uptodate.com

Rofes L, et al. Diagnosis and management of oropharyngeal Dysphagia and its nutritional and respiratory complications in the elderly. *Gastroenterology Research and Practice.* 2011;2011. pii: 818979. Epub 2010 Aug 3.

➤ *Tumours*

ASGE Technology Committee. Endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointestinal Endoscopy* 2008;68:11-18.

Badreddine RJ, et al. Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma. *Clinical Gastroenterology and Hepatology*. 2010;8(3):248-53.

Curvers WL, et al. Novel imaging modalities in the detection of oesophageal neoplasia. *Best Practice & Research Clinical Gastroenterology* 2008; 22(4):687-720.

Das A, et al. Comparison of endoscopic treatment and surgery in early esophageal cancer: An analysis of surveillance epidemiology and end results data. *The American Journal of Gastroenterology* 2008;103:1340-1345

Dubecz A, et al. Modern surgery for esophageal cancer. *Gastroenterology Clinics of North America* 2008;37(4):965-987.

Greenwald BD, et al. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. *Gastrointestinal Endoscopy.* 2010;71(4):686-93.

Hatta w., et al. Optical coherence tomography for the staging of tumor infiltration in superficial esophageal squamous cell carcinoma. *Gastrointestinal Endoscopy.* 2010;71(6):899-906.

Kendall C, et al. Evaluation of Raman probe for oesophageal cancer diagnostics. *Analyst.* 2010;135(12):3038-41.

Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? *Gut* 2005;54:1-5

Okines AF, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for advanced esophagogastric cancer: dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 trial. *Journal of Clinical Oncology.* 2010;28(25):3945-50.

Pouw RE, et al. Successful balloon-based radiofrequency ablation of a widespread early squamous cell carcinoma and high-grade dysplasia of the esophagus: a case report. *Gastrointestinal Endoscopy* 2008;68(3):537-541.

Robertson E, et al. Genetics of Gastroesophageal Cancer: paradigms, Paradoxes and Prognostic Utility. *The American Journal of Gastroenterology* 2008;103:443-449

Shaheen NJ. Advances in Barrett's Esophagus and Esophageal Adenocarcinoma. *Gastroenterology* 2005;128:1554-1566.

Umar SB. Esophageal Cancer: epidemiology, pathogenesis and prevention. *Nature Clinical Practice Gastroenterology & Hepatology*. 2008;5(9):517-526

Veuillez V, et al. Multimodal treatment of oesophageal cancer. *Best Practice & Research Clinical Gastroenterology* 2007;21(6):947-963.

➢ *Miscellaneous*

Caution About Overinterpretation of Symptom Indexes in Reflux Monitoring for Refractory Gastroesophageal Reflux Disease. *Clinical Gastroenterology and Hepatology*. 2011;9:868-874. James C. Slaughter, et al.

Endoscopy Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* 2005;37:570-578.

Goetz M., et al. Confocal laser endomicroscopy in gastrointestinal diseases. *Biophotonics* 2011;4:498-508.

Goetz M and Wang TD. Molecular imaging in gastrointestinal endoscopy. *Gastroenterology.* 2010;138(3):828-33.e1.

Jayasekeran V, et al. Adjunctive functional pharyngeal electrical stimulation reverses swallowing disability after brain lesions. *Gastroenterology.* 2010;138(5):1737-46.

Khashab MA and Kalloo AN. Natural orifice translumenal endoscopic surgery. *Current Opinion in Gastroenterology.* 2010;26(5):471-7.

Kehlet H. Fast-track surgery - an update on physiological care principles to enhance recovery. *Langenbeck's Archive of Surgery* 2005;241:416-423.

Meng W., et al. Downregulation of TGF-beta receptor types II and III in oral squamous cell carcinoma and oral carcinoma-associated fibroblasts. *BMC Cancer* 2011;11:88.

Müller M, et al.Long-term recurrence rates following dilation of symptomatic Schatzki rings. *Digestive Diseases and Sciences.* 2011;56(5):1432-7.

Neumann, H., et al. Confocal laser endomicroscopy: technical advances and clinical applications. *Gastroenterology.* 2010;139:388-392.

Noll L, et al. Pharyngeal flow interval: a novel impedance-based parameter correlating with aspiration. *Journal of Neurogastroenterology and Motility*. 2011;23(6):551-556.

Omari TI, et al. A method to objectively assess swallow function in adults with suspected aspiration. *Gastroenterology.* 2011;140(5):1454-63.

Savin T, et al. On the growth and form of the gut. *Nature.* 2011;476(7358):57-62.

Smith JA, et al. Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. Gastroenterology. 2010;139(3):754-62.

Woodward, T.A., et al. Natural orifice trans-luminal endoscopic surgery in the esophagus. *Gastrointestinal Endoscopy Clinics of North America.* 2010;20:123-138.

Canadian Association of Physicians for the Environment www.cape.ca

Reimann M., et al. Tumor stroma-derived TGF-beta limits myc-driven lymphomagenesis via Suv39h1-dependent senescence. *Cancer Cell* 2010;17:262-272.

STOMACH

➢ *Dysmotility*

Bielefeldt K, et al. Different faces of gastroparesis. *World Journal of Gastroenterology* 2009;15(48):6052-6060.

Camilleri M, et al. Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clinical Gastroenterology and Hepatology* 2011;9:5-12.

Cherian D, et al. Abdominal pain is a frequent symptom of gastroparesis. *Clinical Gastroenterology and Hepatology*. 2010;8(8):676-81.

Di Nardo G. Review article: Molecular, pathological and therapeutic features of human enteric neuropathies. *Alimentary Pharmacology & Therapeutics* 2008;27(9):724-740.

Ejskjaer N, et al. Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic gastroparesis; a randomized, placebo-controlled study. *Neurogastroenterology & Motility* 2010;22:1069-e281.

Grover M, et al. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology*. 2011 May;140(5):1575-85.e8.

Hasler WL. Gastroparesis—current concepts and considerations. Medscape. www.medscape.com

Henderson JM, Boyer TD. Kutner MH, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: A randomised trial. *Gastroenterology* 2006; 130:1643

Kovac AL. Prophylaxis of postoperative nausea and vomiting: controversies in the use of serotonin 5-hydroxytryptamine subtype 3 receptor antagonists. *Journal of Clinical Anesthesia* 2006;18(4):304-318.

McCallum RW, et al. Gastric Electrical Stimulation With Enterra Therapy Improves Symptoms From Diabetic Gastroparesis in a Prospective Study. *Clinical Gastroenterology and Hepatology* 2010 ;8(11):947-54.

Niebyl J R. Nausea and Vomiting in Pregnancy. *The New England Journal of Medicine* 2010;363:1544-1550.

Olden KW. Functional Nausea and vomiting. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(4):202-208.

Park MI, et al. Gastroparesis Clinical Update. *The American Journal of Gastroenterology* 2006;101(5):1129-1139.

Parkman HP, et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. *Gastroenterology*. 2011;140(1):101-15.

Patrick A. Review article: gastroparesis. *Alimentary Pharmacology & Therapeutics* 2008;27(9):724-730

Soffer E, et al. Review Article: Gastric electrical stimulation for gastroparesis- physiological foundations, technical aspects and clinical implications. *Alimentary Pharmacology and Therapeutics* 2009;30:681-694.

Sugumar A. A systematic review of the efficacy of domperidone for the treatment of diabetic gastropathies. *Clinical Gastroenterology and Hepatology* 2008;6(7):726-733

Villanueva C. Current endoscopic therapy of variceal bleeding. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):261-78.

Williams KS. Post operative Nausea and Vomitting. *Surgical Clinics of North America* 2005;85(6):1229-1241.

Yardley JH. Granulomatous gastritis. *UpToDate online journal*. www.uptodate.com

Yardley JH. Hyperplastic Gastropathies and other causes of enlarged folds. *UpToDate online journal*. www.uptodate.com

➢ *Dyspepsia, peptic ulcer disease (PUD), H.Pylori*

Al-Sabah S. Cost-effectiveness of proton-pump inhibition before endoscopy in upper gastrointestinal bleeding. *Clinical Gastroenterology and Hepatology* 2008;6(4):418-425.

Amieva MR. Host-Bacterial Interactions in *Helicobacter pylori* infection. *Gastroenterology* 2008;134:306-323.

Arnold A. Approach to therapy in multiple endocrine neoplasia type 1. UpToDate online encyclopedia. www.uptodate.com

Bektas M, et al. The effect of *Helicobacter pylori* eradication on dyspeptic symptoms, acid reflux and quality of life in patients with functional dyspepsia. *European Journal of Internal Medicine* 2009;20(4):419-423.

Blaser MJ. Does *Helicobacter pylori* protect against asthma and allergy? *Gut* 2008;57(5):561-567.

Bonheur JL. Gastrinoma. *Emedicine online journal*. www.emedicine.com

Chan FKL, et al Peptic-ulcer disease. *Lancet* 2002; 360: 933-941.

Chey WD, et al, Practice Parameters Committee of the American College of Gastroenterology. American College of *Gastroenterology* guideline on the management of *Helicobacter pylori* infection. *The American Journal of Gastroenterology* 2007;102:1808-1825.

Chey WD. American *Gastroenterology* guideline on the management of *Helicobacter pylori* infection. *The American Journal of Gastroenterology* 2007;102(8):1808-1825.

Chiba N, et al. Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment-*Helicobacter pylori* positive (CADET-Hp) randomized controlled trial. *British Medical Journal* 2002 324(7344):1012-1016.

DeLyria, E. S., et al. Vaccine-induced immunity against *Helicobacter pylori* in the absence of IL-17A. *Helicobacter*. 2011; 16(3): 169–178.

Donnellan C, et al. WITHDRAWN: Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database of Systemic Review* 2010 Feb 17;2:CD003245

El-Nakeeb A, et al. Effect of *Helicobacter pylori* eradication on ulcer recurrence after simple closure of perforated duodenal ulcer. *International Journal of Surgery* 2009;7:126-129

Every, A.L., et al. Evaluation of superoxide dismutase from *Helicobacter pylori* as a protective vaccine antigen. *Vaccine*. 2011; 29(7): 1514-1518.

Expert panel on appropriate use of PPIs, NSAIDs, and ASA. Alimentary Pharmacology & Therapeutics2009;29(5):481-96.

Fischbach L. Meta-analysis: effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Alimentary Pharmacology & Therapeutics*2007;26(3):343-357.

Flach, et al. C-F. Proinflammatory cytokine gene expression in the stomach correlates with vaccine-induced protection against *Helicobacter pylori* infection in mice: an important role for interleukin-17 during the effector phase. *Infection and Immunity*. 2011; 79(2): 879-886.

Fletcher EH, et al. Systematic review: *Helicobacter pylori* and the risk of upper gastrointestinal bleeding risk in patients taking aspirin. *Alimentary Pharmacology and Therapeutics*. 2010;32(7):831-9.

Ghassemi KA, et al. Gastric acid inhibition in the treatment of peptic ulcer hemorrhage. *Current Gastroenterology Reports* 2009;11(6):462-469.

Gisbert JP, et al. Review article: *Helicobacter pylori*-negative duodenal ulcer disease. *Alimentary Pharmacology & Therapeutics*; 30:791-815

Graham, DY. et al. *Helicobacter pylori*. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1054.

Grubman, A., et al. The innate immune molecule, NOD1, regulates direct killing of *Helicobacter pylori* by antimicrobial peptides. *Cellular Microbiology*. 2010; 12(5): 626–639.

Guarner J, et al. *Helicobacter pylori* diagnostic tests in children: review of the literature from 1999 to 2009. *European Journal of Pediatrics* 2010;169(1):15-25.

Huang JQ, et al. Role of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002;359(9300):14-22.

Hunt et al. World Gastroenterology Organisation Practice Guidelines: *Helicobacter pylori* in Developing Countries. *WGO*. 2010, 1-14

Hunt R, et al. Canadian Helicobacter Study Group Consensus Conference: Update on the management of *Helicobacter pylori* – an evidence-based evaluation of six topics relevant to clinical outcomes in patients eradicated for H pylori infection. *Canadian Journal of Gastroenterology*2004;18(9):547-554.

Hunt, Richard. Risks of Untreated *H. pylori* Infection. *AGA Institute Post Graduate Course* 2006; pg. 333-342

Jafri N, et al. Meta-analysis: Sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naïve to treatment. *Annals of Internal Medicine* 2008;103:2220-2223

Keller J, et al. The spectrum and treatment of gastrointestinal disorders during pregnancy. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): pg. 433.

Lahner E, et al. Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy. *Alimentary Pharmacology & Therapeutics* 2009*;*29:1219-1229

Lai, L.H., et al. *Helicobacter pylori* and benign upper digestive disease. *Best Practice & Research Clinical Gastroenterology* 2007;21(2):261-279.

Lips CJ. Approach to therapy in multiple endocrine neoplasia type 2. *UpToDate online journal*. www.uptodate.com

Luther JSP, et al. Triple versus quadruple therapy as primary treatment for *Helicobacter pylori* infection: A meta-analysis of efficacy and tolerability. *The American Journal of Gastroenterology*2008; 103:S397.

McColl KE, et al. Randomised trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive H pylori testing alone in the management of dyspepsia. *British Medical Journal* 2002;324(7344):999-1002.

Moayyedi P, et al. An update of the Cochrane systematic review of *Helicobacter pylori* eradication therapy in nonulcer dyspepsia: resolving the discrepancy between systematic reviews. *The American Journal of Gastroenterology*2003;98(12):2621-2626.

Moayyedi P, et al. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database of Systemic Reviews* 2003;(1):CD001960.

Park MI. Gastroparesis Clinical Update. *The American Journal of Gastroenterology* 2006;101(5):112-139.

Peura DA. Association between *Helicobacter pylori* infection and duodenal ulcer. *UpToDate online journal*. www.uptodate.com

Pilotto A, et al. Optimal management of peptic ulcer disease in the elderly. *Drugs Aging.* 2010;27(7):545-58.

Prichard DM. Pathogenesis of gastrinoma associated with multiple endocrine neoplasia type 1. *Emedicine online journal*. www.emedicine.com

Saad RJ, et al. Levofloxacin triple or PPI quadruple salvage therapy for persistent *Helicobacter pylori* infection: Results of a meta-analysis. *The American Journal of Gastroenterology*2006; 101:488-496.

Saad RJ. Persistent *Helicobacter pylori* infection after a course of antimicrobial therapy—what's next? *Clinical Gastroenterology and Hepatology* 2008;6:1086-1090.

Saad RJ. Review article: current and emerging therapies for functional dyspepsia. *Alimentary Pharmacology & Therapeutics*2006;24(3):475-492.

Santacroce L. *Helicobacter pylori* Infection. *Emedicine online journal*; www.emedicine.com

Schubert ML. Control of Gastric Acid Secretion in Health and Disease. *Gastroenterology* 2008;134:1842-1860

Shanks AM, et al. *Helicobacter pylori* infection, host genetics and gastric cancer. *Journal of Digestive Diseases* 2009;10(3):157-164.

Sheu BS, et al. *Helicobacter pylori* colonization of the human gastric epithelium: a bug's first step is a novel target for us. *Journal of Gastroenterology & Hepatology* 2010;25(1):26-32.

Soll AH. Clinical manifestations of peptic ulcer disease. *UpToDate online journal*. www.uptodate.com

Soll AH. Complications of peptic ulcer disease. *UpToDate online journal*. www.uptodate.com

Soll AH. Diagnosis of peptic ulcer disease. *UpToDate online journal* www.uptodate.com

Targownik LE, et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *The American Journal of Gastroenterology* 2009;104(6):1475-1482.

The American Lung Association Asthma Clinical Research Centers. Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma. *The New England Journal of Medicine* 2009;360(15):1487-1499.

Thomson, ABR., et al. Safety of the Long-term Use of Proton Pump Inhibitors (PPI's). *World Journal of Gastroenterology.* 2010; 16(16): 1-8.

Thukral, CC., and Wolf, Jacqueline L. Drugs for gastrointestinal disorders in pregnant women. *Nature Clinical Practice Gastroenterology & Hepatology* 2006;3(5):256.

Varadarajulu S. *Helicobacter pylori*-negative peptic ulcer disease. *UpToDate online journal*. www.uptodate.com

Velin, D., et al. PAR2 promotes vaccine-induced protection against *Helicobacter* infection in mice. *Gastroenterology.* 2011; 141(4): 1273-1282.

Walsh JH, et al. Drug Therapy: The treatment of *Helicobacter pylori* infection in the management of peptic ulcer disease. *The New England Journal of Medicine*1995; 334:984-991.

Wee, J.L.K., et al. Protease-activated receptor-1 down-regulates the murine inflammatory and humoral response to *Helicobacter pylori*. *Gastroenterology.* 2010; 138(2): 573-582.

Wikipedia contributors. MALT Lymphoma. Wikipedia, the free encyclopedia. May 25, 2009 at 17:09. Available at http://en.wikipedia.org/wiki/MALT_lymphoma.

Wikipedia Contributors. Zollinger-Ellison Syndrome. Wikipedia, The Free Encyclopedia. April 29, 2009, at 11:26 UTC. Available at http://en.wikipedia.org/wiki/Zollinger-ellison_syndrome.

William CO, et al. Occurrence of nighttime gastroesophageal reflux in disturbed and normal sleepers. *Clinical Gastroenterology & Hepatology* 2008;6:1099.

Wilson KT. Immunology of *Helicobacter pylori* insights into the failure of the immune response and perspectives on vaccine studies. *Gastroenterology* 2007;133(1):288-308.

Wu CY, et al. Early *Helicobacter pylori* eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009;137:1641-1648

Yardley JH. Metaplastic (chronic) atrophic gastritis. *UpToDate online journal*. www.uptodate.com

Zulio A. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. *Gut* 2007;56:1353-1357

➢ *Non-steroidal anti inflammatory drugs (NSAIDs)*

Abraham NS, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. *Circulation.* 2010 Dec 14;122(24):2619-33.

Abrahamsen B., et al. Proton pump inhibitor use and the antifracture efficacy of alendronate. Archives of Internal Medicine. 2011;171:998-1004.

Arora G, et al. Proton pump inhibitors for gastroduodenal damage related to nonsteroidal anti-inflammatory drugs or aspirin: twelve important questions for clinical practice. *Clinical Gastroenterology and Hepatology* 2009; 7: 725-735.

Bhatt D L, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease. *The New England Journal of Medicine* 2010?;363:1909-17.

Bhatt, D. L, et al. The COGENT Investigators. Clopidogrel with or without omegrazole in coronary artery disease. *The New England Journal of Medicine*.2010;363:1909-1917.

Chan F, et al. Management of patients on nonsteroidal anti-inflammatory drugs: A clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal anti-inflammatory drugs and anti-platelet agents. *The American Journal of Gastroenterology* 2008;103:2908-2918.

Chan F. The David Y. Graham Lecture: Use of Nonsteroidal Antiinflammatory Drugs in a COX-2 restricted environment. *The American Journal of Gastroenterology*2008;103:221-227.

Chan FKL, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (Condor): a randomised trial. *The Lancet* 2010;376:173-179.

Charlot M, et al. Proton-Pump Inhibitors Are Associated With Increased Cardiovascular Risk Independent of Clopidogrel Use. *Annals of Internal Medicine* 2010;153:378-386.

Cryer B, et al. Low-dose aspirin-induced ulceration is attenuated by aspirin-phosphatidylcholine: a randomized clinical trial. *The American Journal of Gastroenterology.* 2011;106(2):272-7.

Desai JC, et al. NSAID-induced antral ulcers are associated with distinct changes in mucosal gene expression. *Alimentary Pharmacology and Therapeutics* 2009;30:71-81.

Earnshaw SR., et al. Cost-Utility of Aspirin and Proton Pump Inhibitors for Primary Prevention. *Archives of Internal Medicine.* 2011; 171(3): 218–225.

Epplein M, et al. Nonsteroidal anti-inflammatory drugs and risk of gastric adenocarcinoma: the multiethnic cohort study. *American Journal of Epidemiology* 2009;170(4):507-514

Feldman M. NSAIDs (including aspirin): Pathogenesis of gastroduodenal toxicity. *UpToDate online journal* 2007; www.uptodate.com

Feldman M. NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity. *UpToDate online journal* 2007; www.uptodate.com

Fujimori S, et al. Distribution of small intestinal mucosal injuries as a result of NSAID administration. *European Journal of Clinical Investigation.* 2010;40(6):504-10.

Giustarini D, et al. Modulation of thiol homeostasis induced by H2S-releasing aspirin. *Free Radical Biology & Medicine .* 2010;48(9):1263-72.

Graham DY. NSAIDs, risks, and gastroprotective strategies: current status and future. *Gastroenterology* 2008;134(4):1240-1246.

Gupta M, Eisen GM. NSAIDs and the gastrointestinal tract. *Current Gastroenterology Reports* 2009;11(5):345-353.

Hunt RH, et al. Recommendations for the ppropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastro- protective agents. *Canadian Journal of Gastroenterology* 2002;16:231-240

Klebl, F.H., et al. Future expectations in the prophylaxis of intestinal bleeding. *Best Practice & Research Clinical Gastroenterology* 2008; 22(2):373-387.

Laine L, et al. Gastric Mucosal defense and cytoprotection: bench to bedside. *Gastroenterology* 2008;135:41-60.

Laine L, et al. Risk factors for NSAID associated upper GI clinical events in a long term prospective study of 34,701 arthritis patients. *Alimentary Pharmacology and Therapeutics* 2010;32:1240-1248.

Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120(3):594-606.

Laine L. Gastric Mucosal defense and cytoprotection: bench to bedside. *Gastroenterology* 2008;135:41-60.

Laine L and Hennekens C. Proton Pump Inhibitor and Clopidogrel Interaction: Fact or Fiction? *The American Journal of Gastroenterology.* 2010; 105:34–41.

Lanas, A. Gastrointestinal bleeding associated with low-dose aspirin use: relevance and management in clinical practice. *Expert Opinion on Drug Safety.*2011;10:45-54.

Lanza FL, et al. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *The American Journal of Gastroenterology* 2009;104:728-738

Lebwohl B, et al. Review: NSAIDs and Cox-2 inhibitors may prevent colorectal cancer but increase gastrointestinal and cardiovascular harm. *American College of Physicians Journal Club* 2007;147(1):15-16.

Lombardo L, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clinical Gastroenterology and Hepatology.* 2010;8(6):504-8.

McCormack JP, et al. Digging for data from the COX-2 trials. *Canadian Medical Association Journal* 2002;166(13):1649-1650.

Mehta SR. Aspirin for Prevention and Treatment of Cardiovascular Disease. *Annals of Internal Medicine* 2009;150:414-416.

Musumba C, et al. Review Article: Cellular and molecular mechanisms of NSAID-induced peptic ulcers. *Alimentary Pharmacology & Therapeutics*2009; 30:517-531

Nema H and Kato M. Comparative study of therapeutic effects of PPI and H2RA on ulcers during continuous aspirin therapy. World Journal of Gastroenterology. 2010;16(42):5342-6.

Ng FH, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. *Gastroenterology.* 2010;138(1):82-8.

Ng SC and Chan FK. PPI therapy: PPI plus aspirin for secondary cardiovascular disease prevention. *Nature Review Gastroenterology & Hepatology.* 2011;8(10):543-5.

Padol IT, et al. Association of myocardial infarctions with COX-2 inhibition may be related to immunomodulation towards a Th1 response resulting in atheromatous plaque instability: an evidence-based interpretation. *Rheumatology (Oxford.* 2010;49(5):837-843.

Pare G, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *The New England Journal of Medicine* 2010;363:1704-1714.

Rainsford KD. Cardiovascular adverse reactions from NSAIDs are more than COX-2 inhibition alone. Rheumatology (Oxford). 2010;49(5):834-836

Rostom A, et al. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. *Alimentary Pharmacology and Therapeutics* 2009;29:481-496.

Rostom A, et al. Gastroduodenal ulcers associated with the use of nonsteroidal anti-inflammatory drugs: a systematic review of preventative pharmacological interventions. Ottawa (ON): Canadian coordinating Office for Health Technology Assessment; 2004. Technology overview No 12.

Rostom A. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. *Alimentary Pharmacology & Therapeutics* 2009;29:481-496.

Rostom A. Gastrointestinal safety of cyclooxygenase-2 inhibitor: a Cochrane Collaboration systematic Review. *Clinical Gastroenterology and Hepatology* 2007;5:818-828.

Saini, S.D., et al. Cost-effectiveness analysis: cardiovascular benefits of proton pump inhibitor co-therapy in patients using aspirin for secondary prevention. *Alimentary Pharmacology & Therapeutics.* 2011;34:243–251.

Scarpignato C and Hunt RH. Nonsteroidal antiinflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis, and prevention. *Gastroenterology Clinics of North America.* 2010;39(3):433-64.

Solomon DH. Overview of selective COX-2 inhibitors. *UpToDate online journal* 2007; www.uptodate.com

Sung JJ, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Annals of Internal Medicine.* 2010;152(1):1-9.

Taha AS, et al. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low dose aspirin (FAMOUS): a phase III, randomised, double blind, placebo-controlled trial. *Lancet* 2009; 374(9684):119-125

Targownik LE, et al. The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. *Gastroenterology* 2008; 134:937-944.

Vaezi MF, et al. Proton pump inhibitor therapy improves symptoms in postnasal drainage. *Gastroenterology* 2010;139:1887-1893.

Van Marrewjik CJ. Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H2-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND study): a primary-care-based randomized controlled trial. *Lancet* 2009;373:215-225.

Wallace JL and Ma L. Inflammatory mediators in gastrointestinal defense and injury. *Experimental Biology and Medicine (Maywood).* 2001;226(11):1003-15.

Wu C-Y, et al. Histamine2-Receptor Antagonists Are an Alternative to Proton Pump Inhibitor in Patients Receiving Clopidogrel. *Gastroenterology* 2010;139:1165-1171.

Zhou Y, et al. Effect of indomethacin on bile acid-phospholipid interactions: implication for small intestinal injury induced by nonsteroidal anti-inflammatory drugs. *American Journal of Physiology Gastrointestinal and Liver Physiology.* 2010; 298(5): G722–G731.

➢ *Acute non-variceal upper GI bleeding (NVUGIB;UGIB)*

Aabakken L. Current endoscopic and pharmacological therapy of peptic ulcer bleeding. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):243-259.

Aabakken Lars. Endoscopic haemostasis. *Best Practice and Research Clinical Gastroenterology* 2008; 22 (5): 899-927

Andriulli A. Proton pump inhibitors and outcomes of hemostasis in bleeding peptic ulcers: a series of meta-analyses. *The American Journal of Gastroenterology* 2005; 100:207-219.

Atkinson RJ, et al. Usefulness of prognostic indices in upper gastrointestinal bleeding. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):233-242.

Barkun A, et al. A one-year economic evaluation of six alternative strategies in the management of uninvestigated upper gastrointestinal symptoms in Canadian primary care. *Can J Gastroenterol.* 2010 Aug;24(8):489-98

Bhatt DL. ACCF/ACG/AHA 2008 expert consensus document on reducing the Gastrointestinal risks of antiplatelet therapy and NSAID use. *The American Journal of Gastroenterology* 2008;103:2890-2907

British Society of *Gastroenterology* Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. *Gut* 2005; 51(Suppl IV):iv1-iv6.

Button L A, et al. Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study. *Alimentary Pharmacology and Therapeutics* 2011;33:64-76.

Chan FK, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *The New England Journal of Medicine* 2002;347(26):2104-2110.

Cheung J, et al. Peptic ulcer bleeding outcomes adversely affected by end-stage renal disease. *Gastrointestinal Endoscopy* 2010;71:44.

Conrad SA, et al. Randomized double blind comparison of immediate release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Criicalt Care Medicine* 2005;33:760-765.

Cook DJ, et al. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage : a meta-analysis. *Gastroenterology* 1992;102:139-148.

Dall M, et al. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clinical Gastroenterology and Hepatology* 2009;7:1314-1321.

Dall M, et al. There is an association between selective serotonin reuptake inhibitor use and uncomplicated peptic ulcers: a population-based case-control study. *Alimentary Pharmacology and Therapeutics* 2010;32:1383-1391.

de Franchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology.* 2005;43:167–176.

Enestvedt BK, et al. An evaluation of endoscopic indications and findings related to nonvariceal upper GI hemorrhage in a large mulitcenter consortium. *Gastrointestinal Endoscopy* 2008;67:422-429.

Hearnshaw S. The role of blood transfusion in the management of upper and lower intestinal tract bleeding. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):335-371.

Heil U, et al. The patient with recidivent obscure gastrointestinal bleeding. *Best Practice & Research Clinical Gastroenterology* 2007;21(3):393-407.

Henderson JM, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systemic shunt for variceal bleeding: A randomized trial. *Gastroenterology* 2006;130:1643-1651.

Howden CW, et al. Early infusion of high-dose omperazole before endoscopy reduced the need for endoscopic therapy. *American College of Physicians Journal Club* 2007;147(1):18.

Julapalli VR. Appropriate use of intravenous proton pump inhibitors in the management of Bleeding peptic ulcer. *Digestive Disease and Sciences* 2005;50(7):1185-1193.

Kafes AJ, et al. Clinical outcomes after double-balloon enteroscopy in patients with obscure GI bleeding and a positive capsule endoscopy. *Gastrointestinal Endoscopy* 2007;66(2):304-309

Laine L, et al. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. *Clinical Gastroenterology & Hepatol ogy* 2009:33-47

Lanas A, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *The American Journal of Gastroenterology* 2009:1633

Lin KJ, et al. Acid suppressants reduce risk of gastrointestinal bleeding in patients on antithrombotic or anti-inflammatory therapy. *Gastroenterology.* 2011;141(1):71-9.

Raju GS. American Gastroenterological Association (AGA) Institute Technical Review on Obscure Gastrointestinal Bleeding. *Gastroenterology* 2007;133:1697-1717.

Schrier SL. Approach to the adult patient with anemia. *UpToDate online journal* 2007; www.uptodate.com

Schrier SL. Causes and diagnosis of anemia due to iron deficiency. *UpToDate online journal* 2007; www.uptodate.com

Straube S, et al. Mortality with upper gastrointestinal bleeding and perforation: effects of time and NSAID use. *BMC Gastroenterology* 2009;9:41

Sung JJY, et al. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding. *American College of Physicians* 2009:455

Targownik LE, et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *The American Journal of Gastroenterology* 2009; 104(6):1475-1482.

Van Rensburg C. Clinical trial: intravenous pantoprazole vs. ranitidine for the prevention of peptic ulcer rebleeding: a multicentre, multinational, randomized trial. *Alimentary Pharmacology & Therapeutics* 2009;29:497-507.

Veitch AM. Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures. *Gut* 2008;57:1322-1329.

Wang CH, et al. High-dose vs non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials. *Archives of Internal Medicine*. 2010;170(9):751-8.

Wong RCK. Nonvariceal upper gastrointestinal hemorrhage: Probing beneath the surface. *Gastroenterology* 2009;137:1897-1911

Wu CY, et al. Histamine$_2$ receptor antagonists are an alternative to proton pump inhibitor in patients receiving clopidogrel. *Gastroenterology* 2010;139:1165-1171.

Wu CY, et al. Long-term peptic ulcer rebleeding risk estimation in patients undergoing haemodialysis: a 10-year nationwide cohort study. *Gut.* 2011;60(8):1038-42.

Yachimski PS. Gastrointestinal Bleeding in the Elderly. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(2):80-93

➤ *Bariatric Surgery*

Buchwald H, et al. Bariatric surgery: A systematic review and meta-analysis. *JAMA* 2004;292:1724-1737.

Bueter M, et al. [Why patients lose weight after bariatric operations]. *Zentralbl Chir*. 2010;135(1):28-33.

Decker GA, et al. Gastrointestinal and Nutritional Complications after Bariatric Surgery. *The American Journal of Gastroenterology* 2007;102:2571-2580.

DeVault KR, et al. Insights into the future of gastric acid suppression. *Nat. Rev. Gastroenterol Hepatol* 2009;6:524

Elder KA, et al. Bariatric Surgery: A Review of Procedures and Outcomes. *Gastroenterology* 2007;132:2253-2271.

Gertler R, et al. Pouch vs. No pouch following total gastrectomy: meta-analysis and systematic review. *The American Journal of Gastroenterology 2010;*105(5):1208.

Jeffrey D. Mosko and Geoffrey C. Ngyen. Increased Perioperative Mortality Following Bariatic Surgery Among Patients With Cirrhosis. *Clinical Gastroenterology and Hepatology* 2011;9:897-901.

Lau DC. Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. *Canadian Medical Association Journal* 2007;176(8 Suppl):S1-13.

Laville M, Disse E. Bariatric surgery for diabetes treatment: why should we go rapidly to surgery. *Diabetes & Metabolism.* 2009;35(6 Pt 2):562-563.

Mathus-Vliegen E.M, et al. The role of endoscopy in bariatric surgery. *Best Practice and Research Clinical Gastroenterology* 2008; 22 (5): 839-864.

Nguyen NT, et al. Complications of antiobesity surgery. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(3):138-147.

O'Brien PE, et al. Laparoscopic adjustable gastric banding in severely obese adolescents: a randomized trial. *Journal of American Medical Association* 2010;303(6):519-526.

Scholmerich J. Postgastrectomy syndromes-diagnosis and treatment. *Best Practice and Research Clinical Gastroenterology* 2004:18(5);917-933.

Talley NJ. Is there an increased risk of hip fracture in patients on long-term PPI therapy? *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(8):420-421

Thomson ABR. Dumping Syndrome. *Emedicine online journal*. www.Emedicine.com

Tsesmeli N, et al. The future of bariatrics: endoscopy, endoluminal surgery, and natural orifice transluminal endoscopic surgery. *Endoscopy.* 2010;42(2):155-162

Vetter ML, et al. Narrative Review: Effect of Bariatric Surgery on Type 2 Diabetes Mellitus. *Annals of Internal Medicine* 2009;150:94-103.

Wolfe BM. Bariatric Surgery: A review of Procedures and Outcomes. *Gastroenterology* 2007;132:2253-2271

Woodward G, et al. Bariatric Surgery (CH 7). Sleisenger & Bordtran's Gastrointestinal and Liver Disease.

➢ *Gastritis and Gastric Neoplasia*

Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376(9742):687-97.

Bergholt MS, et al. Characterizing variability in in vivo Raman spectra of different anatomical locations in the upper gastrointestinal tract toward cancer detection. *Journal of Biomedical Optics.* 2011;16(3):037003.

Bianchi LK. Fundic Gland polyp dysplasia is common in familial adenomatous polyposis. *Clinical Gastroenterology and Hepatology* 2008;6:180-185.

Boers JE, et al. HER2 status in gastro-oesophageal adenocarcinomas assessed by two rabbit monoclonal antibodies (SP3 and 4B5) and two in situ hybridization methods (FISH and SISH). *Histopathology.* 2011;58(3):383-94.

Carmack SW, et al. Management of gastric polyps: a pathology-based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol* 2009;6(6):331-341

Carmack SW, et al. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. *The American Journal of Gastroenterology* 2009;104(6): 524-532.

Chiu HF, et al. Statins are associated with a reduced risk of gastric cancer: a population-based case-control study. *The American Journal of Gastroenterology.* 2011;106(12):2098-103.

Correa P. Carcinogenesis of *Helicobacter pylori. Gastroenterology* 2007;133:656-672.

De Vita F, et al. Human epidermal growth factor receptor 2 (HER2) in gastric cancer: a new therapeutic target. *Cancer Treatment Reviews.* 2010;36 Suppl 3:S11-5.

De Vries AC et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 2008;134:945-952.

De Vries AC. *Helicobacter pylori* eradication for the prevention of gastric cancer. *Alimentary Pharmacology & Therapeutics* 2007;26(Suppl 2):25-35

Ehata S, et al. Transforming growth factor-β decreases the cancer-initiating cell population within diffuse-type gastric carcinoma cells. *Oncogene* .2011;30: 1693-1705.

Frank L, et al. Quigley and the Practice Parameters Committee of the American College of Gastroenterology. *The American Journal of Gastroenterology* 2009; 104:728

Han SW, et al. Epidermal growth factor receptor intron 1 CA dinucleotide repeat polymorphism and survival of advanced gastric cancer patients treated with cetuximab plus modified FOLFOX6. *Cancer Science.* 2010;101(3):793-9.

Huang Z, et al. In vivo detection of epithelial neoplasia in the stomach using image-guided Raman endoscopy. *Biosensors and Bioelectronics.* 2010;26(2):383-9.

Huh WJ, et al. XBP1 controls maturation of gastric zymogenic cells by induction of MIST1 and expansion of the rough endoplasmic reticulum. *Gastroenterology.* 2010;139(6):2038-49.

Jørgensen JT. Targeted HER2 treatment in advanced gastric cancer. *Oncology.* 2010;78(1):26-33.

Kahrilas PJ, et al. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1392-1413

Kato M, et al. Magnifying endoscopy with narrow-band imaging achieves superior accuracy in the differential diagnosis of superficial gastric lesions identified with white-light endoscopy: a prospective study. *Gastrointestinal Endoscopy.* 2010;72(3):523-9.

Kim C, et al. A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. *Investigational New Drugs*. 2011;29(2):366-73.

Kim, Y.H., et al. Randomized phase II study of nimotuzumab, an anti-EGFR antibody, plus irinotecan in patients with 5-fluorouracil-based regimen-refractory advanced or recurrent gastric cancer in Korea and Japan: Preliminary results. Journal of Clinical Oncology. *29(Suppl. 4), a87(2011)*

Laville M, et al. Bariatric surgery for diabetes treatment: why should we go rapidly to surgery. *Diabetes & Metabolism* 2009;35(6 Pt 2):562-563.

Lenz, H.J., et al. Lapatinib + capecitabine in advanced gastric cancer: an open-label, phase II study of non-ErbB2-targeted disease. *Annals of Oncology*. 21(Suppl.8), a817P (2010).

Li CQ and Li YQ. Endomicroscopy of intestinal metaplasia and gastric cancer. Gastrointestinal Clinics of North America. 2010;39(4):785-96.

Metz DC, et al. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 2008;135(5):1469-1492.

Moayyedi P. An update of the Cochrane Systematic Review of *Helicobacter pylori* Eradication Therapy in Nonulcer Dyspepsia: Resolving the Discrepancy Between Systematic Reviews. *The American Journal of Gastroenterology*2003;98(12):2621-2627.

O'Brien PE, et al. Laparoscopic adjustable gastric banding in severely obese adolescents: a randomized trail. *Journal of American Medical Association* 2010;303(6):519-526.

Rao S, et al. Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study. *Annals of Oncology.* 2010;21(11):2213-9.

Roukos DH. Innovative genomic-based model for personalized treatment of gastric cancer. *Expert Review of Molecular Diagnostics* 2008;8(1):29-39.

Sepulveda AR. Chronic Gastritis. *Emedicine online journal*. www.emedicine.com

Snyder RH. Acute Gastritis. *Emedicine online journal*. www.emedicine.com

Tack J, et al. Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nature Reviews Gastroenterology and Hepatology* 2009;6:583-590

Tack J. Functional duodenal Disorders. *Gastroenterology* 2006;130:1466-1479

Tsesmeli N, Coumaros D. The future of bariatrics: endoscopy, endoluminal surgery, and natural orifice transluminal endoscopic surgery. *Endoscopy* 2010;42(2):155-162

Vanden Berghe P, et al Contribution of different triggers to the gastric accommodation reflex in man. *American Journal of Physiology Gastrointestinal and Liver Physiology.* 2009 Sep 10. [Epub ahead of print]

Wainberg ZA, et al. Lapatinib, a dual EGFR and HER2 kinase inhibitor, selectively inhibits HER2-amplified human gastric cancer cells and is synergistic with trastuzumab in vitro and in vivo. *Clinical Cancer Research.* 2010;16(5):1509-19.

Wehbi M. Acute Gastritis. *Emedicine online journal*. www.emedicine.com

Wikipedia Contributors. Atrophic Gastritis. Wikipedia, the free encyclopedia. April 17, 2009 at 17:11 UTC. Available at: http://en.wikipedia.org/wiki/ Atrophic_gastritis

Wikipedia contributors. Menetrier's Disease. Wikipedia, the free encyclopedia. December 21, 2008 at 17:58. Available at http://en.wikipedia.org/wiki/M%C3%A9n%C3%A9trier%27s_disease.

Yamamoto H. Technology insight: endoscopic submucosal dissection of gastrointestinal neoplasms. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(9):511-520.

Yardley JH. Acute and chronic gastritis due to *Helicobacter pylori*. *UpToDate online journal*. www.uptodate.com

➢ *Miscellaneous*

Kiesslich R, et al. New imaging techniques and opportunities in endoscopy. *Nature Review Gastroenterology & Hepatology*.2011;8:547-553.

Philip Wai Yan Chiu, et al. Transgastric endoluminal gastrojejunostomy: technical development from bench to animal study (with video). *Gastrointestinal Endoscopy.* 2010;71:390-393.

Ramachandran, R., et al. Neutrophil elastase acts as a biased agonist for proteinase-activated receptor-2 (PAR$_2$). *The Journal of Biological Chemistry*. 2011; 286: 24638-24648.

SMALL INTESTINE

> ### Small intestine bacterial overgrowth syndrome

AGA. AGA Technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464-1486

Balfour SR, et al. Microbial influences in inflammatory bowel diseases. *Gastroenterology* 2008;134:577-594.

Cogan TA. Norepinephrine increases the pathogenic potential of Campylobacter jejuni. *Gut* 2007;56(8):1060-1065.

Dupont HL. Bacterial Diarrhea. *The New England Journal of Medicine* 2009; 361:1560-1569

Dupont HL. Systematic Review: prevention of travellers' diarrhoea. *Alimentary Pharmacology & Therapeutics* 2008;27:741-751

DuPont HL. Travelers' diarrhea: antimicrobial therapy and prevention. *Nature Clinical Practice Gastroenterology & Hepatology* 2005;2(4):191-198.

Glass RI, et al. Norovirus Gastroenteritis. *The New England Journal of Medicine* 2009; 361:1776-1785.

Hasler WL. Gastroparesis-current concepts and considerations. Medscape. www.medscape.com

Leder K. Epidemiology, clinical manifestatiosn and diagnosis of giardiasis. *UpToDate online journal*. www.uptodate.com

Nesh P. Microbes in Gastrointestinal Health and Disease. *Gastroenterology* 2009;136:65-80

O'Hara AM, et al. Gut Microbiota: Mining for Therapeutic Potential. *Clinical Gastroenterology and Hepatology* 2007;5(3):274-284.

Palmer C, et al. Development of the human infant intestinal microbiota. *PLoS Biology* 2007;5(7)e177.

Pande C. Small-intestinal bacterial overgrowthin cirrhosis related to the severity of liver disease. *Alimentary Pharmacology & Therapeutics* 2009;29:1273-1281

Patrick A. Review article: gastroparesis. *Alimentary Pharmacology & Therapeutics* 2008;27(9):724-730

Poly F. Pathogenesis of Campylobacter. *Current Opinion in Gastroenterology* 2008;24(1):27-31.

Post DJ. Immunosuppression in Liver Transplantation. *Liver Transplantation* 2005;11(11):1307-1314

Shanahan F. Probiotics in perspective. *Gastroenterology* 2010;139:1808-1812.

Smout AJ, et al. Gastrointestinal motility testing. *Best Practice & Research, Clinical Gastroenterology* 2009;23(3):287-298.

Soffer E, et al. Review Article: Gastric electrical stimulation for gastroparesis- physiological foundations, technical aspects and clinical implications. *Alimentary Pharmacology & Therapeutics* 2009;30:681-694

Sokol H. Specificities of the fecal microbiota in inflammatory bowel disease. *Inflammatory Bowel Disease* 2006;12(2):106-111.

Sugumar A. A systematic review of the efficacy of domperidone for the treatment of diabetic gastropathies. *Clinical Gastroenterology and Hepatology* 2008;6(7):726-733

Szarka LA, et al. Methods for measurement of gastric motility. *American Journal of Physiology Gastrointestinal and Liver Physiology* 2009;296(3):G461-75.

Tack J, et al; Medscape. Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nature Reviews Gastroenterology and Hepatology* 2009;6(10):583-590.

Vanden Berghe P, et al. Contribution of different triggers to the gastric accommodation reflex in man. *American Journal of Physiology Gastrointestinal and Liver Physiology* 2009 ;

Vanner S. The small intestinal bacterial overgrowth. Irritable bowel syndrome hypothesis: implications for treatment. *Gut* 2008;57:1315-1321.

Wikipedia contributors. Giardiasis. *Wikipedia, the free encyclopedia*. 2009 at 05:38 UTC. Available at http://en.wikipedia.org/wiki/Giardiasis.

Williams KS. Post operative Nausea and Vomitting. *Surgical Clinics of North America* 2005;85(6):1229-41.

> ### *Intestinal gas and bloating*

Atia AN, et al. Oral rehydration solutions in non-cholera diarrhea: A review. *The American Journal of Gastroenterology* 2009 advance online publication.

Azpiroz F. Intestinal gas dynamics: mechanisms and clinical relevance. *Gut* 2005;54:893-895.

Black DD. Development and physiological regulation of intestinal lipid absorption: cellular event in chylomicron assembly in secretion. *American Journal of Physiology- Gastrointestinal and Liver Physiology.* 2007;293(3):G519-24

Carey EJ, et al. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. *The American Journal of Gastroenterology* 2007;102:89-95.

Cellier C. Obscure gastrointestinal bleeding: Role of video-capsule and double balloon enteroscopy. *Best Practice & Research Clinical Gastroenterology* 2008;22:329-340.

Chen X, et al. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel disease. *World J Gastroenterol* 2007;13:4372-4378.

Chitkara DK. Lactose intolerance. *UptoDate online journal* 2007. www.uptodate.com

de Leusse A, et al. Capsule endoscopy or push enteroscopy for first-line exploration of obscure gastrointestinal bleeding? *Gastroenterology* 2007;132(3):855-856.

Di Nardo G. Molecular, pathological and therapeutic features of human enteric neuropathies. *Alimentary Pharmacology & Therapeutics* 2008;28(1):25-42.

Fletcher JG. Computerized tomography enterography and its role in small-bowel imaging. *Clinical Gastroenterology and Hepatology* 2008;6:283-289.

Gabrielli A. Scleroderma. *The New England Journal of Medicine* 2009;360(19):1989-2003.

Gerson LB, et al. Complications associated with double balloon enteroscopy at nine US centers. Clinical Gastroenterology and Hepatology 2009;7:1177-1182.

Gerson LB. Outcomes associated with deep enteroscopy. *Gastrointestinal EndoscopyClin N Am*. 2009;19(3):481-496

Hoffman K M, et al. Duodenal neuroendocrine tumors: classification, functional syndromes, diagnosis and medical treatment. *Best Practice & Research Clinical Gastroenterology* 2005; 19(5):675-697.

Huizinga JD, et al. Physiology, injury, and recovery of interstitial cells of cajal: basic and clinical science. *Gastroenterology* 2009;137:1548-1556

Huprich JE, et al. Obscure gastrointestinal bleeding: Evaluation with 64-section multiphase CT enterography-Initial experience. *Radiology* 2008;246:562-571

Kafes AJ, et al. Clinical outcomes after double-balloon enteroscopy in patients with obscure GI bleeding and a positive capsule endoscopy. *Gastrointestinal Endoscopy*. 2007;66(2):304-309.

Koretz RL. AGA technical review on parenteral nutrition. *Gastroenterology* 2001;121:970-1001.

Maglinte DD. Small-bowel obstruction: State-of-the-Art Imaging and its role in clinical management. *Clinical Gastroenterology and Hepatology* 2008;6:130-139

Medical Council of Canada. Chronic Diarrhea. http://mcc.ca/Objectives_Online/

Nightingale J. Guidelines for the management of patients with a short bowel. *Gut* 2006;55 Suppl 4:iv1-12.

O'Keefe SJD. Short Bowel Syndrome and Intestinal Failure: Consensus Definitions and Overview. *Clinical Gastroenterology & Hepatology* 2006;4:6-10.

Palmer C. Development of the human infant intestinal microbiota. *PLoS Biology* 2007;5(7)e177.

Papadia C. Plasma Citrulline Concentration: A reliable marker of small bowel absorptive capacity independent of intestinal inflammation. *The American Journal of Gastroenterology* 2007;102(7):1474-1482.

Pasha SF, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: A meta-analysis. *Clinical Gastroenterology & Hepatology* 2008;6:671-676.

Rondonotti E, et al. Small bowel capsule endoscopy in 2007: Indications, risks and limitations. *World J Gastroenterol* 2007;13:6140-6149.

Schroy PC. Clinical presentation and diagnosis of gastrointestinal lymphomas. *UpToDate online journal*. www.uptodate.com

Sudan DL. Treatment of intestinal failure: intestinal transplantation. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(9):503-510

Viazis N, et al. Is there a role for second-look capsule endoscopy in patients with obscure GI bleeding after a nondiagnostic first test? *Gastrointestinal Endoscopy* 2009;69(4):850-856.

➢ *Celiac Disease*

AGA Institute Medical Position Statement on the diagnosis and management of celiac disease. *Gastroenterology* 2006; 131: 1977-1980.

Agardh D. Antibodies against synthetic deamidated gliadin peptides and tissue transglutaminase for the identification of childhood celiac disease. *Clinical Gastroenterology and Hepatology* 2007;5:1276-1281.

Akram A. Adult autoimmune enteropathy: Mayo Clinic Rochester Experience. *Clinical Gastroenterology and Hepatology* 2007;5:1282-1290.

Anjum N, et al. Maternal celiac disease autoantibodies bind directly to syncytiotrophoblast and inhibit placental tissue transglutaminase activity. *Reproductive Biology and Endocrinology* 2009;7:16.

Apstein MD. Whipple's Disease. UpToDate online journal. www.uptodate.com

Ashorn S, et al. Serological responses to microbial antigens in celiac disease patients during a gluten-free diet. *Journal of Clinical Immunology* 2009;29(2):190-195.

Baldassarre M, et al. Celiac disease: pathogenesis and novel therapeutic strategies. *Endocr ine, Metabolic & Immune Disorders Drug Targets* 2008;8(3):152-158.

Basso D, et al. Antibodies against synthetic deamidated gliadin peptides for celiac disease diagnosis and follow-up in children. *Clinical Chemistry* 2009;55(1):150-157.

Bassotti G, et al Antroduodenojejunal motor activity in untreated and treated celiac disease patients. *Journal of Gastroenterology & Hepatology* 2008;23(7 Pt 2):e23-28.

Bergamaschi G, et al. Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. *Haematologica* 2008;93(12):1785-1791.

Bernardo D, et al. Higher constitutive IL15R alpha expression and lower IL-15 response threshold in coeliac disease patients. *Clinical and Experimental Immunology* 2008;154(1):64-73.

Bertini I, et al. The metabonomic signature of celiac disease. *Journal of Proteome Research.* 2009;8(1):170-177.

Bethune MT, et al. Interferon-gamma released by gluten-stimulated celiac disease-specific intestinal T cells enhances the transepithelial flux of gluten peptides. *Journal of Pharmacology and Experimental Therapeutics* 2009;329(2):657-668.

Biagi F, et al. The prevalence and the causes of minimal intestinal lesions in patients complaining of symptoms suggestive of enteropathy: a follow-up study. *Journal of Clinical Pathology* 2008;61(10):1116-1118.

Bonamico M, et al. Società Italiana di Gastroenterologica, Epatologia, e Nutrizione Pediatrica. Duodenal bulb biopsies in celiac disease: a multicenter study. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(5):618-622.

Bracken S, et al. Altered gene expression in highly purified enterocytes from patients with active coeliac disease. *BMC Genomics* 2008;9:377.

Broide E, et al. Evidence for aberrant regulation of MAP kinase signal transduction pathway in peripheral blood mononuclear cells in patients with active celiac disease. *Digestive Diseases and Sciences* 2009;54(6):1270-1275.

Brooks D. Cash, et al. The Prevalence of Celiac Disease Among Patients With Nonconstipated Irritable Bowel Syndrome Is Similar to Controls. *Gastroenterology* 2011;141:1187-1193.

Cammarota G, et al. Optimal band imaging system: a new tool for enhancing the duodenal villous pattern in celiac disease. *Gastrointestinal Endoscopy* 2008;68(2):352-357.

Campanella J, et al. Clinical response to gluten withdrawal is not an indicator of coeliac disease. *Scandinavian Journal of Gastroenterology* 2008;43(11):1311-1314.

Caputo I, et al. Tissue transglutaminase in celiac disease: role of autoantibodies. Amino Acids. 2009;36(4):693-699.

Carroccio A, et al. Clinical symptoms in celiac patients on a gluten-free diet. *Scandinavian Journal of Gastroenterology* 2008;43(11):1315-1321.

Castellanos-Rubio A, et al. TH17 (and TH1) signatures of intestinal biopsies of CD patients in response to gliadin. *Autoimmunity* 2009;42(1):69-73.

Chang M, et al. Genetic testing before serologic screening in relatives of patients with celiac disease as a cost containment method. *Journal of Clinical Gastroenterology* 2009;43(1):43-50.

Chitkara DK. Lactose intolerance. *UptoDate online journal* 2007. www.uptodate.com

Ciacci C, et al. Urinary stone disease in adults with celiac disease: prevalence, incidence and urinary determinants. *The Journal of Urology* 2008;180(3):974-979.

Ciaccio EJ, et al. Quantitative assessment of the degree of villous atrophy in patients with coeliac disease. *Journal of Clinical Pathology* 2008;61(10):1089-1093.

Cianci R, et al. Abnormal synthesis of IgA in coeliac disease and related disorders. J Biol Regul Homeost Agents. 2008;22(2):99-104.

Ciclitira PJ. Management of Coeliac Disease in Adults. *UpToDate online Journal* 2007. www.uptodate.com

Collado MC, et al. Imbalances in faecal and duodenal Bifidobacterium species composition in active and non-active coeliac disease. *BMC Microbiology* 2008;8:232.

Cummins AG, et al. Morphometric evaluation of duodenal biopsies in celiac disease. *The American Journal of Gastroenterology 2011*;106:145-150.

Daum S, et al. Refractory coelic disease. *Best Practice & Research Clinical Gastroenterology* 2005;19(3):413-424.

Dema B, et al. The IL6-174G/C polymorphism is associated with celiac disease susceptibility in girls. *Human Immunology* 2009;70(3):191-194.

Di Cagno R, et al. Use of selected sourdough strains of Lactobacillus for removing gluten and enhancing the nutritional properties of gluten-free bread. *Journal of Food Protection* 2008;71(7):1491-1495.

Di Sabatino A, et al. Evidence for the role of interferon-alpha production by dendritic cells in the Th1 response in Celiac Disease. *Gastroenterology* 2007;133:1175-1187.

Dickey W, et al. Homocysteine and related B-vitamin status in coeliac disease: Effects of gluten exclusion and histological recovery. *Scandinavian Journal of Gastroenterology* 2008;43(6):682-688.

Donat E, Planelles D, et al. Allelic distribution and the effect of haplotype combination for HLA type II loci in the celiac disease population of the Valencian community (Spain). *Tissue Antigens* 2009;73(3):255-261.

Dørum S, et al. A quantitative analysis of transglutaminase 2-mediated deamidation of gluten peptides: implications for the T-cell response in celiac disease. *Journal of Proteome Research.* 2009;8(4):1748-1755.

Dubois PC, et al. Translational mini-review series on the immunogenetics of gut disease: immunogenetics of coeliac disease. *Clinical and Experimental Immunology* 2008;153(2):162-173.

Dugan JM, et al. The liver in celiac disease. *Alimentary Pharmacology and Therapeutics* 2005;21:515-518.

Ehren J, et al. Protein engineering of improved prolyl endopeptidases for celiac sprue therapy. *Protein Engineering, Design & Selection* 2008;21(12):699-707.

Einarsdottir E, et al. IL23R in the Swedish, Finnish, Hungarian and Italian populations: association with IBD and psoriasis, and linkage to celiac disease. *BMC Medical Genetics* 2009;10:8.

Elfström P, et al. Risk of thyroid disease in individuals with celiac disease. *The Journal of Clinical Endocrinology and Metabolism* 2008; 93(10):3915-3921.

El-Salhy M., et al. The prevalence of celiac disease in patients with irritable bowel syndrome. *Molecular Medicine Reports* 2011;4:403-405.

Emami MH, et al. How frequent is celiac disease among epileptic patients? *The Journal of Gastrointestinal Liver Diseases* 2008;17(4):379-382.

Ersoy O, et al. Capsule endoscopy findings in celiac disease. *Digestive Diseases and Sciences* 2009;54(4):825-829.

Fabris A, et al. HLA-G 14bp deletion/ insertion polymorphism in celiac disease. *The American Journal of Gastroenterology* 2011;106:139-144.

Farrell RJ, et al. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2010.

Fenollar F. Whipple's Disease. *The New England Journal of Medicine* 2007;356:55-66.

Ford AC. Meta-analysis: yield of diagnostic tests for celiac disease in dyspepsia. *Alimentary Pharmacology & Therapeutics* 2009;30:28-36

Ford A.C., et al. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Archives of Internal Medicine* 2009;169:651-658.

Frank DN, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel disease. *Proceedings of the National Academy of Sciences of the United States of America* 2007;104(34):13780-1385.

Freeman HJ, et al. The small intestine. *First Principles of Gastroenterology* 2005.

Freeman HJ. Adult celiac disease in the elderly. *World Journal of Gastroenterology* 2008;14(45):6911-6914.

Freeman HJ. Neurological disorders in adult celiac disease. *Canadian Journal of Gastroenterology* 2008;22(11):909-911.

Freeman HJ. Pearls and pitfalls in the diagnosis of adult celiac disease. *Canadian Journal of Gastroenterology* 2008; 22(3):273-280.

Fröhlich-Reiterer EE, et al. DPV-Wiss Study Group. Screening frequency for celiac disease and autoimmune thyroiditis in children and adolescents with type 1 diabetes mellitus--data from a German/Austrian multicentre survey. *Pediatric Diabete.* 2008;9(6):546-553.

Gao Y. Increased risk for non-hodgkin lymphoma in individuals with celiac disease and a potential familial association. *Gastroenterology* 2009;136:91-96.

Gass J, et al. Combination enzyme therapy for gastric digestion of dietary gluten in patients with Celiac Sprue. *Gastroenterology* 2007;133:472-480.

Giangreco E, et al. Prevalence of celiac disease in adult patients with refractory functional dyspepsia: value of routine duodenal biopsy. *World Journal of Gastroenterology* 2008; 14(45):6948-6953.

Gibson PR. Fructose malabsorption and the bigger picture. *Alimentary Pharmacology & Therapeutics* 2007;25(4):349-363

Goosenberg E. Collagenous and lymphocytic colitis. *eMedicine Journal* 2006; 7(2). www.emedicine.com/med/topic1351.htm

Granzotto M, et al. Regulatory T-cell function is impaired in celiac disease. *Digestive Diseases and Sciences* 2009;54(7):1513-1519.

Greco L, et al. Safety for patients with celiac disease of baked goods made of wheat flour hydrolysed during food processing. *Clinical Gastroenterology and Hepatology* 2011;9:24-29.

Green PHR, et al. An association between microscopic colitis and celiac disease. *Clinical Gastroenterology and Hepatology* 2009;7:1210-1216.

Green PHR, et al. Coeliac disease. *The Lancet* 2003; 362:383–391.

Group. Canadian consensus guidelines on long-term nonsteroidal anti-inflammtory drug therapy and the need for gastroprotection: benefits versus risks. *Alimentary Pharmacology & Therapeutics* 2009;29(5):481-496.

Guariso G. Clinical, Subclinical and potential autoimmune diseases in an Italian population of children with celiac disease. *Alimentary Pharmacology & Therapeutics* 2007;26(10):1409-1417.

Hadjivassiliou M, et al. Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. *Annals of Neurology* 2008;64(3):332-343.

Haines ML, et al. Systematic Review: the evidence for long-term management of celiac disease. *Alimentary Pharmacology and Therapeutics* 2008;28:1042-1066.

Hallert C, et al. Clinical trial: B vitamins improve health in patients with coeliac disease living on a gluten-free diet. *Alimentary Pharmacology & Therapeutics* 2009;29(8):811-816.

Harris KM, et al. Cutting edge: IL-1 controls the IL-23 response induced by gliadin, the etiologic agent in celiac disease. *Journal of Immunology* 2008;181(7):4457-4460.

Hawkey CJ. Nonsteroidal anti-inflammatory drug gastropathy. *Gastroenterology* 2000;119(2):521-535.

Heyman R, et al. Effect of a gluten-free diet on bone mineral density in children with celiac disease. *Gastroenterologie Clinique et Biologique* 2009;33(2):109-114.

Hull CM, et al. Elevation of IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis. *The British Jouranl of Dermatology* 2008;159(1):120-124.

Jadresin O, et al. Compliance with gluten-free diet in children with coeliac disease. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(3):344-348.

Jatla M, et al. Anthropometric, serologic, and laboratory correlation with villous blunting in pediatric celiac disease: diabetics are different. *Journal of Clinical Gastroenterology* 2009;43(7):622-626.

Jatla M, et al. Bone mineral content deficits of the spine and whole body in children at time of diagnosis with celiac disease. *Journal of Pediatric Gastroenterology and Nutrition* 2009;48(2):175-180.

Johnson MW, et al. Celiac disease in the elderly. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(12):697-706.

Karwautz A, et al. Eating pathology in adolescents with celiac disease. *Psychosomatics* 2008;49(5):399-406.

Kasarda DD, et al. Surface-associated proteins of wheat starch granules: suitability of wheat starch for celiac patients. *Journal of Agricultural Food Chemistry* 2008;56(21):10292-10302.

Katz K.D., et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. *The American Journal of Gastroenterology* 2011;106:1333-1339.

Kaukinen K. Latent Coeliac disease or celiac disease beyond villous atrophy? *Gut* 2007; 56(10):1339-1340

Kavuncu V, et al. Is there any requirement for celiac disease screening routinely in postmenapausal women with osteoporosis? Rheumatol Int. 2009;29(7):841-845.

Kemppainen TA, et al. Unkilned and large amounts of oats in the coeliac disease diet: a randomized, controlled study. *Scandinavian Journal of Gastroenterology* 2008;43(9):1094-1101.

Koskinen L, et al. Cost-effective HLA typing with tagging SNPs predicts celiac disease risk haplotypes in the Finnish, Hungarian, and Italian populations. Immunogenetics. 2009;61(4):247-256.

Kurppa K, et al. Diagnosing mild enteropathy celiac disease: A Randomized, controlled clinical study. *Gastroenterology* 2009;136:816-823.

LaMont JT. Tropical Sprue. UpToDate online Journal www.uptodate.com

Larsson K, et al. Skåne Study Group. Annual screening detects celiac disease in children with type 1 diabetes. *Pediatric Diabete.* 2008;9(4 Pt 2):354-359.

Leach ST, et al. Coeliac disease screening in children: assessment of a novel anti-gliadin antibody assay. *Journal of Clinical Laboratory Analysis* 2008;22(5):327-333.

Leffler DA, et al. A simple validated gluten-free diet adherence survey for adults with celiac disease. *Clinical Gastroenterology & Hepatology* 2009;7(5):530-536.

Leffler DA, et al. Update on serologic testing in celiac disease. *The American Journal of Gastroenterology* 2010;105:2520-2524.

Leffler DA. A Prospective comparative study of five measures of gluten-freediet adherence with celiac disease. *Alimentary Pharmacology & Therapeutics* 2007;26(9):1227-1235

Legroux-Gérot I, et al. Screening for celiac disease in patients with osteoporosis. Joint Bone Spine. 2009;76(2):162-165.

Lester DR. Gluten measurement and its relationship to food toxicity for celiac disease patients. Plant Methods. 2008;4:26.

Lewy H, et al. Seasonality of birth month of children with celiac disease differs from that in the general population and between sexes and is linked to family history and environmental factors. *Journal of Pediatric Gastroenterology and Nutrition* 2009;48(2):181-185.

Li M, et al. A report on the International Transglutaminase Autoantibody Workshop for Celiac Disease. *The American Journal of Gastroenterology* 2009;104(1):154-163.

Lohi S. Increasing prevalence of celiac disease over time. *Alimentary Pharmacology & Therapeutics* 2007;26(10):1409-1417.

Longobardi T. Utilization of Health-Care Resources by patients with IBD in Manitoba: A profile of time since diagnosis. *The American Journal of Gastroenterology* 2007;102:1683-1691.

Ludvigsson JF, et al. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. *BMC Gastroenterology* 2009;9:19.

Maiden L, et al. A blinded pilot comparison of capsule endoscopy and small bowel histology in unresponsive celiac disease. *Digestive Diseases and Sciences* 2009;54(6):1280-1283.

Malamut G, et al. Presentation and Long-Term Follow-up of Refractory Celiac Disease Comparison of Type I with Type II. *Gastroenterology* 2009;136:81-90.

Marietta EV, et al. Correlation analysis of celiac sprue tissue transglutaminase and deamidated gliadin IgG/IgA. *World Journal of Gastroenterology* 2009;15(7):845-848.

Matysiak-Budnik T. Long-Term follow-up of 61 coeliac patients diagnosed in childhood: evolution toward latency is possible on a normal diet. Gut 2007;56(10):1379-1386

Matysiak-Budnik T., et al. In vivo real-time imaging of human duodenal mucosal structures in celiac disease using endocytoscopy. *Endoscopy* 2010;42:191-196.

Megiorni F, et al. HLA-DQ and risk gradient for celiac disease. *Human Immunology* 2009;70(1):55-59.

Milovec V. Clinical features and diagnosis of malabsorption. UpToDate online journal 2007; www.uptodate.com

Monsuur AJ, de Bakker PI, Zhernakova A, et al. Effective detection of human leukocyte antigen risk alleles in celiac disease using tag single nucleotide polymorphisms. *PLoS One* 2008;3(5):e2270.

Morón B, Bethune MT, Comino I, et al. Toward the assessment of food toxicity for celiac patients: characterization of monoclonal antibodies to a main immunogenic gluten peptide. *PLoS One* 2008;3(5):e2294.

Muram-Zborovski T, et al. Primary intestinal intraepithelial natural killer-like T-cell lymphoma: case report of a distinct clinicopathologic entity. *Archives of Pathology & Laboratory Medicine* 2009;133(1):133-137.

Nachman F, et al. Quality of life in celiac disease patients: prospective analysis on the importance of clinical severity at diagnosis and the impact of treatment. *Digestive Liver Disease* 2009;41(1):15-25.

Nassef HM, et al. Electrochemical immunosensor for detection of celiac disease toxic gliadin in foodstuff. *Analytical Chemistry* 2008;80(23):9265-9271.

Nemes E, et al. Gluten intake interferes with the humoral immune response to recombinant hepatitis B vaccine in patients with celiac disease. *Pediatrics* 2008;121(6):e1570-1576.

Nenna R, et al. HLA-DQB1*02 dose effect on RIA anti-tissue transglutaminase autoantibody levels and clinicopathological expressivity of celiac disease. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(3):288-292.

Olsson C, et al. Regional variation in celiac disease risk within Sweden revealed by the nationwide prospective incidence register. *Acta Paediatrica* 2009;98(2):337-342.

Olsson C, et al. The everyday life of adolescent coeliacs: issues of importance for compliance with the gluten-free diet. *Journal of Human Nutrition and Dietetics* 2008;21(4):359-367.

Ortega Páez E, et al. Prevalence of dental enamel defects in celiac patients with deciduous dentition: a pilot study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2008;106(1):74-78.

Peltola M, et al. Hippocampal sclerosis in refractory temporal lobe epilepsy is associated with gluten sensitivity. *Journal of Neurology Neurosurgery and Psychiatry* 2009;80(6):626-630.

Piazzi L, et al. Progetto Celiachia-S.I.E.D. Group. Diagnostic value of endoscopic markers for celiac disease in adults: a multicentre prospective Italian study. *Minerva Gastroenterologica Dietologica* 2008;54(4):335-346.

Pinier M, et al. Polymeric binders suppress gliadin-induced toxicity in the intestinal epithelium. *Gastroenterology* 2009;136(1):288-298.

Pinier M, et al. Prevention measures and exploratory pharmacological treatments of celiac disease. *The American Journal of Gastroenterology* 2010;105:2551-2561.

Pividori MI, et al. Electrochemical immunosensor for the diagnosis of celiac disease. *Analytical Biochemistry* 2009;388(2):229-234.

Plot L, et al. Infectious associations of Celiac disease. *Autoimmunity Reviews* 2009;8(4):316-319.

Pope R, et al. Celiac disease during pregnancy: to screen or not to screen? *Archives of Gynecology and Obstetrics* 2009;279(1):1-3.

Prasad KK, et al. Lymphocytic gastritis and celiac disease in indian children: evidence of a positive relation. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(5):568-572.

Raivio T, et al. Comparison of a novel whole blood transglutaminase-based ELISA with a whole blood rapid antibody test and established conventional serological celiac disease assays. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(5):562-567.

Rakhimova M, et al. In vitro differentiation of human monocytes into dendritic cells by peptic-tryptic digest of gliadin is independent of genetic predisposition and the presence of celiac disease. *Journal of Clinical Immunology* 2009;29(1):29-37.

Rostom A. American Gastroenterological Association (AGA) Institute Technical Review on the Diagnosis and Management of Celiac Disease. *Gastroenterology* 2006;131:1981–2002.

Rostom A. Canadian Association of Gastroenterology Consensus

Rubio-Tapia A, et al Celiac disease and persistent symptoms. *Clinical Gastroenterology and Hepatology* 2011;9:13-17.

Rubio-Tapia A. Clinical Staging and survival in refractory celiac disease: A single center experience. Gastroenterology 2009;136:99-107.

Salentijn EM, et al. Tetraploid and hexaploid wheat varieties reveal large differences in expression of alpha-gliadins from homoeologous Gli-2 loci. *BMC Genomics* 2009;10:48.

Sanz Y. Novel perspectives in celiac disease therapy. *Mini Reviews in Medicinal Chemistry* 2009;9(3):359-367.

Sapone A., et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Medicine* 2011;9:23.

Schmidt KJ, et al. Clinical Trial: cyclophosphamide pulse therapy—a promising therapeutic alternative in refractory celiac disease. *Alimentary Pharmacology and Therapeutics* 2009;29:1230-1239.

Schuppan D. Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults. *UpToDate online journal*. www.uptodate.com

Setty M, et al. Celiac disease: risk assessment, diagnosis, and monitoring. *Molecular Diagnosis & Therapy* 2008;12(5):289-298.

Silano M, et al. Antagonist peptides of the gliadin T-cell stimulatory sequences: a therapeutic strategy for celiac disease. *Journal of Clinical Gastroenterology* 2008;42 Suppl 3 Pt 2:S191-192.

Silverster JA. Long-Term follow-up of individuals with celiac disease: an evaluation of current practice guidelines. *Canadian Journal of Gastroenterology* 2007;21(9):557-564.

Simula MP, et al. Two-dimensional gel proteome reference map of human small intestine. *Proteome Science* 2009;7:10.

Skovbjerg H, et al. Deamidation of gliadin peptides in lamina propria: implications for celiac disease. *Digestive Diseases and Sciences* 2008;53(11):2917-2924.

Smyth DJ, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. *The New England Journal of Medicine* 2008;359(26):2767-2777.

Souayah N, et al. Effect of intravenous immunoglobulin on cerebellar ataxia and neuropathic pain associated with celiac disease. *European Journal of Neurology* 2008;15(12):1300-1303.

Soyer P, et al. Celiac disease in adults: evaluation with MDCT enteroclysis. AJR Am J Roentgenol. 2008;191(5):1483-1492.

Stamnaes J, et al. The propensity for deamidation and transamidation of peptides by transglutaminase 2 is dependent on substrate affinity and reaction conditions. *Biochimica et Biophysica Acta* 2008;1784(11):1804-1811.

Stevens L, et al. Gluten-free and regular foods: a cost comparison. *Canadian Journal of Dietetic Practice and Research* 2008;69(3):147-150.

Tang F, et al. Cytosolic PLA2 is required for CTL-mediated immunopathology of celiac disease via NKG2D and IL-15. *The Journal of Experimental Medicine* 2009;206(3):707-719.

Tanner GJ, et al. Dissecting the T cell response to hordeins in celiac disease can develop barley with reduced immunotoxicity. *Alimentary Pharmacology and Therapeutics* 2010;32:1184-1191.

Theis VS, et al. Review article: minimizing tuberculosis anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2008;27:19-30.

Thia KT, et al. Defining the optimal response criteria for the Crohn's disease activity index for induction studies in patients with mildly to moderately active crohn's disease. *The American Journal of Gastroenterology* 2008;103(12):3123-31.

Thia KT, et al. Risk factors associated with progression to intestinal complications of Crohn's disease in a population based cohort. *Gastroenterology* 2010;139:1147-1155.

Thomas HJ, et al. Pneumococcal infection in patients with coeliac disease. *European Journal of Gastroenterology & Hepatology* 2008;20(7):624-628.

Thompson T, et al. Commercial assays to assess gluten content of gluten-free foods: why they are not created equal. *Journal of the American Dietetic Association* 2008;108(10):1682-1687.

Tjon J.M.-L., et al. Celiac disease: how complicated can it get? *Immunogenetics* 2010;62:641-651.

Tjon JM, et al. Defective synthesis or association of T-cell receptor chains underlies loss of surface T-cell receptor-CD3 expression in enteropathy-associated T-cell lymphoma. *Blood* 2008;112(13):5103-5110.

Tolone C, et al. A common CTLA4 polymorphism confers susceptibility to autoimmune thyroid disease in celiac children. *Digestive and Liver Disease* 2009;41(6):385-389.

Tosco A, et al. Immunoglobulin A anti-tissue transglutaminase antibody deposits in the small intestinal mucosa of children with no villous atrophy. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(3):293-298.

Upton MP. "Give us this day our daily bread"--evolving concepts in celiac sprue. *Archives of Pathology & Laboratory Medicine* 2008;132(10):1594-1599.

van den Broeck HC, et al. A modified extraction protocol enables detection and quantification of celiac disease-related gluten proteins from wheat. *Journal of Chromatography B, Analytical Technologies in the Biomedical Life Sciences* 2009;877(10):975-982

van Dommelen P, et al. Screening rules for growth to detect celiac disease: a case-control simulation study. *BMC Pediatrics* 2008;8:35.

van Doorn RK, et al. CDDUX: a disease-specific health-related quality-of-life questionnaire for children with celiac disease. *Journal of Pediatric Gastroenterology and Nutrition* 2008;47(2):147-152.

van Heel DA, et al. Recent advances in coeliac disease. *Gut* 2006;55:1037-1046.

Vande Voort JL, et al. Lymphocytic duodenosis and the spectrum of celiac disease. Am J Gastroenterol. 2009;104(1):142-148.

Vécsei AK, et alFollow-up of adult celiac patients: which noninvasive test reflects mucosal status most reliably? *Endoscopy* 2009;41(2):123-128.

Verbeek WH, et al. Incidence of enteropathy--associated T-cell lymphoma: a nation-wide study of a population-based registry in The Netherlands. *Scandinavian Journal of Gastroenterology* 2008;43(11):1322-1328.

Verbeek WH, et al. The presence of small intestinal intraepithelial gamma/delta T-lymphocytes is inversely correlated with lymphoma development in refractory celiac disease. *The American Journal of Gastroenterology* 2008;103(12):3152-3158.

Vermeulen BA, et al. Phenotypic variance in childhood coeliac disease and the HLA-DQ/DR dose effect. *Scandinavian Journal of Gastroenterology* 2009;44(1):40-45.

Vivas S, et al. Age-related clinical, serological, and histopathological features of celiac disease. *The American Journal of Gastroenterology* 2008;103(9):2360-2365.

Volta U. Pathogenesis and clinical significance of liver injury in celiac disease. *Clinical Reviews in Allergy & Immunology* 2009;36(1):62-70.

Walker M.M., et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population based study. *Gastroenterology* 2010;139:112-119.

West J. Celiac Disease and Its Complications: A time traveler`s perspective. *Gastroenterology* 2009;136:32-48.

Wiesner M, et al. Dominance of an alternative CLIP sequence in the celiac disease associated HLA-DQ2 molecule. *Immunogenetic.* 2008;60(9):551-555.

Wikipedia contributors. Coeliac Disease. Wikipedia, the free Encyclopedia. August 16, 2009 at 13:34 UTC. Available at http://en.wikipedia.org/wiki/Coeliac_disease.

Wikipedia contributors. Enteropathy-associated T-cell lymphoma. Wikipedia, the free encyclopedia. August 11, 2009 at 09:31 UTC. Available at http://en.wikipedia.org/wiki/Enteropathy-associated_T-cell_lymphoma.

Wikipedia Contributors. Whipple's Disease. Wikipedia, the free encyclopedia. August 11, 2009 at 11:47. Available at http://en.wikipedia.org/wiki/Whipple%27s_disease

Wikipedia Contributors.Tropical Sprue. Wikipedia, the free encyclopedia. June 26, 2009 at 16:24 UTC. Available at http://en.wikipedia.org/wiki/Tropical_sprue.

Wolters VM. Genetic Background for celiac disease and its clinical implications. *The American Journal of Gastroenterology* 2008;103(1):190-195.

Wouters J, et al. Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down syndrome. *The Journal of Pediatrics* 2009;154(2):239-242.

Wright JM, Perry TL, Bassett KL et al. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA* 2001;286(19):2398-400.

Zanchi C, et al. Bone metabolism in celiac disease. *The Journal of Pediatrics* 2008;153(2):262-265.

➢ *Crohn Disease*

Abraham C, et al. Inflammatory bowel disease. *The New England Journal of Medicine* 2009;361(21): 2066-2078.

Abreau MT, et al. Diagnosis of colitis: Making the Initial diagnosis. *Clinical Gastroenterology and Hepatology* 2007;5(3):295-301.

Akobeng AK. The evidence base for interventions used to maintain remissions in Crohn's Disease. *Alimentary Pharmacology and Therapeutics* 2008;27(1):11-8.

Alfadhli AA, et al. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Systemic Review* 2005;CD003459.

Aratari A, et al. Early versus late surgery for ileo-caecal Crohn's disease. *Alimentary Pharmacology and Therapeutics* 2007;26(10):1303-12.

Ardizzone S, et al. How long is it advisable to prolong maintenance treatment of patients with ulcerative colitis? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S238-239.

Baidoo L, et al. Radiologic Testing in Crohn's Disease. *Inflammatory Bowel Disease* 2008;14 Suppl 2:S181-2 2008.

Barrett JC, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nature Genetics* 2008;40(8):955-962.

Baumgart DC, et al. Inflammatory bowel disease: Cause and immunobiology. *Lancet* 2007;369(9573): 1627-1640.

Baumgart DC, et al. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;369(9573):1641-1657.

Beaugerie L, et al. Predictors of Crohn's Disease. *Gastroenterology* 2006;130(3):650-656.

Bebb JR, et al. How effective are the usual treatments for Crohn's disease? *Alimentary Pharmacology and Therapeutics* 2004;15;20(2):151-159.

Bernstein C.N. IBD: Trying to optimize a tool to measure disability in IBD. *Nature Reviews Gastroenterology and Hepatology* 2011;8:478-480.

Bernstein C.N., et al. A prospective population-based study of triggers of symptomatic flares in IBD. *The American Journal of Gastroenterology* 2010;105:1994-2002.

Biancone L, et al. Treatment with biologic therapies and the risk of cancer in patients with IBD. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;2(4):78-91.

Boureille A, et al. Role of small bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009;41:618-637.

Burakoff R., et al. Blood-based biomarkers can differentiate ulcerative colitis from crohn's disease and noninflammatory diarrhea. *Inflammatory Bowel Disease* 2011;17:1719-1725.

Carrascosa P, et al. CT colonoscopy in inflammatorybowel disease. *Abdominal Imaging* 2007;32:596-601.

Chan S., et al. Aspirin in the aetiology of Crohn's disease and ulcerative colitis: a European prospective cohort study. *Alimentary Pharmacology and Therapeutics* 2011;34(6):649-655.

Chermesh I, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Digestive Diseases and Sciences* 2007;52:385-389.

Chiorean MV, et al. Correlation of CT enteroclysis with surgical pathology in Crohn's disease. *The American Journal of Gastroenterology* 2007;102:2541-2550.

Cho JH, et al. The genetics of inflammatory bowel disease. *Gastroenterology* 2007;133:1327-1339.

Clara I., et al. The Manitoba IBD index: evidence for a new and simple indicator of IBD activity. *The American Journal of Gastroenterology* 2009;104:1754-1763.

Coelho J., et al. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESEME Study. *International journal in gastroenterology* 2011;60(2):198-203.

Colombel JF et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52-65.

Colombel JF, et al. Infliximab, Azathioprine, or combination therapy for Crohn's disease. *The New England Journal of Medicine* 2010;362 (15):1383-95.

Colombel JFet al. The Safety Profile of Infliximab in Patients with Crohn's Disease: The Mayo Clinic Experience in 500 Patients. *Gastroenterology* 2004; 126:19–31.

Cornish J, et al. A meta analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007;56:830-837.

Cottone M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti tumor necrosis factor therapy for inflammatory bowel disease. *Clinical Gastroenterology and Hepatology* 2011;9:30-35.

Crissey M.A., et al. Cdx2 levels modulate intestinal epithelium maturity and Paneth cell development. *Gastroenterology* 2011;140:517-528.

D.E. Loomes, et al. Health care resource use and costs for Crohn's disease before and after infliximab therapy. *The Canadian Journal of Gastroenterology* 2011;25(9):497-502.

D'Haens G, et al. Early Combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomized trial. *The Lancet* 2008;371(9613):660-7.

Danese S, et al. Inflammation and coagulation in Inflammatory Bowel disease: The clot thickens. *The American Journal of Gastroenterology* 2007;102:174-186.

Daperno M, et al. Prospective study of the effects of concomitant medications on thiopurine metabolism in inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2009;30: 843-853.

De Boer NKH, et al. Drug Insight: pharmacology and toxicity of thiopurine therapy in patients with IBD. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(12):686-694.

De Carpi J.M. Psychosocial features of inflammatory bowel disease in the pediatric age group: acceptance of and adaptation to the disease. *Journal of Gastroenterology and Hepatology* 2009;32 (suppl 2):25.

De Schepper HU, et al. Gastrointestinal sensory and motoro disturbances in inflammatory bowel disease—clinical relevance and pathophysiological mechanisms. *Alimentary Pharmacology and Therapeutics* 2008;27(8):621-637.

Eaden JA, et al. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002; 51(Suppl V):v10–v12.

East JE, et al. A pilot study of infrastricture steroid versus placebo injection after balloon dilation of Crohn's strictures. *Clinical Gastroenterology & Hepatology* 2007;5:1065-1069.

Edward V. Loftus Jr., et al. Increased Risks of Developing Anxiety and Depression in Young Patients With Crohn's Disease. *The American Journal of Gastroenterology* 2011;106:1670-1677.

Egberts J.H., et al. Preoperative risk evaluation of postoperative morbidity in IBD patients – impact of the POSSUM score. *International Journal of Colorectal Disease* 2011;26:783-792.

Evstatiev R., et al. FERGlcor, a randomized controlled trial for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011;141(3):846-853.

Feagins LA, et al. Sexual and Reproductive Issues for Men with Inflammatory Bowel Disease. *The American Journal of Gastroenterology* 2009;104:768-773.

Forbes A. Is there a role for multidrug therapy in active Crohn's disease? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S257-258.

Frank DN. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel disease. *Proceedings of the National Academy of Sciences of the United States of America* 2007;104(34):13780-5.

Freeman HJ. Application of the Montreal classification for Crohn's disease to a single clinician database of 1015 patients. Canadian *Journal of Gastroenterology* 2007;21:363-366.

Freeman HJ. Application of the Vienna classification for Crohn's disease to a single clinician database of 877 patients. *Canadian Journal of Gastroenterology* 2001;15:89-93.

Freeman HJ. Granuloma-positive Crohn's disease. *Canadian Journal of Gastroenterology* 2007;21:583-587.

Freeman HJ. Natural history and clinical behaviour of Crohn's disease extending beyond two decades. *Journal of Clinical Gastroenterology* 2003;37:216-219

Freeman HJ. Temporal and geographic evolution of longstanding Crohn's disease over more than 50 years. Canadian *Journal of Gastroenterology* 2003;17:696-700.

Friedman S, et al. Management of neoplastic polyps in inflammatory bowel disease. *Inflammatory Bowel Disease* 2003;9:260-266.

Friedman S. Medical therapy and birth outcomes in women with Crohn's disease: what should we tell our patients? *The American Journal of Gastroenterology* 2007;102:1414-1416.

Froslie KF, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegina-based cohort. *Gastroenterology* 2007;133:412-422.

Geboes K, et al. Indeterminate colitis: a review of the concept – what's in a name? Inflamm Bowel Dis. 2008;14:850-857.

Gebos K. What Histologic Features Best Differentiate Crohn's Disease from Ulcerative Colitis? 2008.

Geier, M. S., et al. Inflammatory bowel disease: Current insights into pathogenesis and new therapeutic options; probiotics, prebiotics and synbiotics. *International Journal of Food Microbiology* 2007. 115(1):1-11.

Gionchetti P, et al. Oral budenoside in the treatment of chronic refractory pouchitis. *Alimentary Pharmacology & Therapeutics* 2007; 25: 1231-1236.

Gionchetti P, et al. Which therapies are advisable in pouchitis? Inflammatory Bowel Disease 2008;14 Suppl 2:S241-242.

Glickman J, et al. Does Rectal Sparing ever Occur in Ulcerative Colitis? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S166-7.

Gomollon F. and Gisbert J.P. IBD: Intravenous iron in IBD – what's the best preparation? *Nature Reviews Gastroenterology and Hepatology* 2011;8:477-478.

Goodhand J.R., et al. Prevalence and management of anemia in children, adolescents, and adults with inflammatory bowel disease. *Inflammatory Bowel Disease* 2011 May 20.

Gopal L. Crohn disease. eMedicine Journal, Oct 4 2005; 6(10). www.emedicine.com/med/topic477.htm

Goyette P, et al. Molecular pathogenesis of inflammatory bowel disease: genotypes, phenotypes and personalized medicine. *Annals of Medicine* 2007;39:177-199.

Graff L.A., et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflammatory Bowel Diseases* 2010 Dec 22.

Grainge M.J., et al. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010;375:657-663.

Greenley R.N., et al. A meta-analysis review of the psychosocial adjustment of youth with inflammatory bowel disease. *Journal of Pediatric Psychology* 2010;35:857-869.

Greydanus D., et al. Suicide risk in adolescents with chronic illness: implications for primary care and specialty pediatric practice: a review. *Developmental Medicine and Child Neurology* 2010;52:1083-1087.

Hanauer SB, et al. European evidence-based consensus on the diagnosis and management of Crohn's Disease. *Gut* 2007;56(2):161-3.

Hanauer SB. Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities. *Inflammatory Bowel Disease* 2006;12(Suppl 1): S3-9.

Hanauer SB. Life after the sonic boom-do immunomodulators really matter when using biologics? *ACG Annual Scientific Meeting Symposia Sessions 2009*:16-18.

Hartman C, et al. Nutritional status and nutritional therapy in inflammatory bowel diseases. *World Journal of Gastroenterology* 2009;15(21): 2570-2578.

Heetun ZS, et al. Reproduction in the patient with Inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2007;26(4):513-33.

Horsthuis K, et al. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: Meta analysis of prospective studies. *Radiology* 2008;247(1):64-79.

Huibregtse, I., et al.. Immunopathogenesis of IBD: Insufficient suppressor function in the gut? *British Medical Journal* 2007;56(4):584.

Irving PM, et al. Appropriate use of corticosteroids in Crohn's Disease. *Alimentary Pharmacology and Therapeutics* 2007;26(3):313-29.

Issa M, et al. Impact of *Clostridium difficile* on inflammatory bowel disease. *Clinical Gastroenterology & Hepatology* 2007;5:345-351.

Itzkowitz SH, et al. Consensus conference: colorectal cancer screening and surveillance in inflammation bowel disease. *Inflammatory Bowel Disease* 2005;11:314-321.

Izcue, A., et al. Interleukin-23 restrains regulatory T cell activity to Drive T cell-dependent colitis. *Immunity* 2008;28(4): 559-570.

Javier P. Gisbert. Safety of Immunomodulators and Biologics for the Treatment of Inflammatory Bowel Disease During Pregnancy and Breast-feeding. *Inflammatory Bowel Disease*. 2010;16:881–895.

Jean Frederic Colombel, et al. Early Mucosal Healing With Infliximab Is Associated With Improved Long-term Clinical Outcomes in Ulcerative Colitis. *Gastroenterology* 2011;141:1194-1201.

Johnson MW, et al. Feacal calprotectin: a noninvasive diagnostic tool and marker of severity in pouchitis. *European Journal of Gastroenterology &* Hepatology 2008;20(3):174-179.

Jones DT, et al. Passive smoking and inflammatory bowel disease: A meta-analysis. *The American Journal of Gastroenterology* 2008;103(12):2382-2393.

Kandiel A, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; 54: 1121-1125.

Kane S, et al. Higher incidence of abnormal pap smears in women with inflammatory bowel disease. *The American Journal of Gastroenterology* 2008;103:631-636.

Kane S, et al. The role of breastfeeding in postpartum disease activity in women with inflammatory bowel disease, *The American Journal of Gastroenterology* 2005; 100:102-105.

Kane S. What are the Minimal Requirements for a Diagnosis of Inflammatory Bowel Disease? *Inflammatory Bowel Disease* 2008;14 Suppl 2: S148-149.

Kaser A. and Blumberg R.S. Autophagy, microbial sensing, endoplasmic reticulum stress, and epithelial function in inflammatory bowel disease. *Gastroenterology* 2011;140:1738-1747.

Kiesslich R, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterology* 2007;132:874-882.

Kiesslich R, et al. What New Endoscopic Imaging Modalities Will Become Important in Diagnosis of IBD. *Inflammatory Bowel Disease* 2008; 14 Suppl 2:S172-176.

Klionsky DJ, et al. Crohn's Disease, Autophagy, and the Paneth cell. *The New England Journal of Medicine* 2009;360(19):1989-2003.

Kohn A. Is there a role for infliximab in severe ulcerative colitis? The European experience. *Inflammatory Bowel Disease* 2008;14 Suppl 2:S234-235.

Kotlyar DS, et al. A systematic review of factors that contribute to hepatosplenic T cell lymphoma in patients with inflammatory bowel disease. *Clinical Gastroenterology and Hepatology* 2011;9:36-41.

Kugathasan S, et al. Searching for new clues in Inflammatory Bowel Disease: Tell tales from pediatric IBD natural history studies. *Gastroenterology* 2008;135(4):1038-1041.

Lashner B. Should Patients with Crohn's Disease be in Colonoscopic Surveillance Programs? *Inflammatory Bowel Disease* 2008; 14 Suppl 2:S192-193.

Lee S.S., et al. Crohn disease of the small bowel: comparison of CT enterography, MR enterography, and small-bowel follow-through as diagnostic techniques. *Radiology* 2009;251:751-761.

Lees CW, et al. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2007;26(3):411-419.

Levenstein S. Could stress play a role in IBD? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S206-207

Lewis JD, et al. Immunosuppressant medications and mortality in Inflammatory Bowel Disease. *The American Journal of Gastroenterology* 2008;103(12):1428-1435.

Lichtenstein GR, et al. American Gastroenterological Association Institute Technical Review on Corticosteroids, Immunomodulators, and Infliximab in Inflammatory Bowel Disease. *Gastroenterology* 2006;130:940–987.

Lichtenstein GR, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clinical Gastroenterology & Hepatology* 2006;4:621-630.

Lichtiger S, et al. The choice trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Alimentary Pharmacology and Therapeutics* 2010;32:1228-1239.

Lievin-Le Moal, V, et al. The front line of enteric host defense against unwelcome intrusion of harmful microorganisms: Mucins, antimicrobial peptides, and microbiota. *Clinical Microbiology Reviews* 2006;19(2):315.

Linda A. Feagins, et al. Current Strategies in the Management of Intra-abdominal Abscesses in Crohn's Disease. *Clinical Gastroenterology and Hepatology* 2011;9:842-850.

Lochs, H. Basics in clinical nutrition: Nutritional support in inflammatory bowel disease. *The European e-Journal of Clinical Nutrition and Metabolism* 2009; 5: e100–e103.

Longobardi T, et al. Utilization of Health-Care Resources by patients with IBD in Manitoba: A profile of time since diagnosis. *The American Journal of Gastroenterology* 2007;102:1683-1691.

Lucendo, AJ, et al. Importance of nutrition in inflammatory bowel disease. World Journal of Gastroenterology 2009;15(17):2081-2088.

Ma C, et al. Systematic review: the short term and long term efficacy of adalimumab following discontinuation of infliximab. *Alimentary Pharmacology and Therapeutics* 30: 977-986.

MacDermott RP. Immunomodulator therapy in Crohn's disease. UptoDate online journal 2007; www.uptodate.com

Magro F and Portela F.Management of inflammatory bowel disease with infliximab and other anti-tumor necrosis factor alpha therapies. *BioDrugs*. 2010 Dec 14;24 Suppl 1:3-14. doi: 10.2165/11586290-000000000-00000.

Mahadevan U, et al. Pregnancy outcomes in women with inflammatory bowel disease: A large community based study from Northern California. *Gastroenterology* 2007;133:1106-1112.

Manitoba: a population-based study. *The American Journal of Gastroenterology*. 2010; 105: 2588–2596.

Marcus S.B., et al. Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clinical Gastroenterology and Hepatology* 2009;7:554-561.

Mark T. Osterman, Et al. No Increased Risk of Myocardial Infarction Among Patients With Ulcerative Colitis or Crohn's Disease. *Clinical Gastroenterology and Hepatology* 2011;9:875-880.

Martin DR, et al. Utility of Magnetic resonance imaging in small bowel Crohn's disease. *Gastroenterology* 2007;133:385-390.

Mason A., et al. Effect of testosterone therapy for delayed growth and puberty in boys with inflammatory bowel disease. *Hormone Research in Paediatrics* 2011;75:8-13.

McGovern D, et al. The IL23 axis plays a key role in the pathogenesis of IBD. *Gut* 2007;56:1333-1336.

Meucci G. What is the Incidence, Prevalence, and Natural History of Indeterminate Colitis? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S159-160 .

Mizoguchi, A, et al. Inflammatory bowel disease, past, present and future: Lessons from animal models. *Journal of Gastroenterology* 2008;43(1):1-17.

Molnar T., et al. Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case-control study. *Scandinavian Journal of Gastroenterology* 2010;45(11):1302-1306.

Morales A, et al. *Inflammatory Bowel Disease* 2007;13:380-1385.

Morales A, et al. Relationship between 6-mercaptopurine dose and 6-thioguanine nucleotide levels in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases* 2007;13:380-385.

Mudter J, et al. Apoptosis of T cells and the control of inflammatory bowel disease: therapeutic implications. *Gut* 2007;56(2):293-303.

Nakahigashi M. and Yamamoto T. Increases in body mass index during infliximab therapy in patients with Crohn's disease: an open label prospective study. *Nature Reviews Gastroenterology and Hepatology* 2011;8:537.

Ng SC, et al. Management of postoperative Crohn's Disease. *The American Journal of Gastroenterology* 2008;103(4):1029-35.

Nguyen G.C., et al. Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. *Gastroenterology* 2011;141:90-97.

Nielsen OH, et al. Diagnosis and management of fistulizing Crohn's disease. *Nature Clinical Practice Gastroenterology & Hepatology* 2009;6(2):92-106.

Nielsen OH, et al. Drug Insight: aminosalicylates for the treatment of IBD. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(3):160-70.

Nikolau S, et al. Diagnostics of inflammatory bowel disease. *Gastroenterology* 2007;133(5):1670-89.

Noomen CG, et al. Update on genetics in inflammatory disease. Genetic Testing in Gastroenterology. *Best Practice & Research Clinical Gastroenterology* 2009;23(2):233-243.

Novacek G et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology* 2010 Sept;139:779.
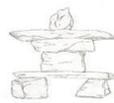
Novak K, et al. Medical Induction of active Crohn's Ileitis: evidence-based management. *Inflammatory Bowel Disease* 2008;14 Suppl 2:S247-248.

Oostlander AE, et al. Histomorphometric analysis reveals reduced bone mass and bone formation in patients with quiescent Crohn's disease. *Gastroenterology* 2011;140:116-123.

Palmon R, et al. What is the Role and Significance of Serum and Stool Biomarkers in the Diagnosis of IBD? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S187-189.

Panaccione R, et al. Adalimumab maintains long-term remission in moderately to severely active Crohn's disease after infliximab failure: 1-year follow-up of gain trial. *Journal of Crohn's and Colitis Supplements* 2008; 2(1):6-7.

Paulsen SR, et al. CT enterography: Non-invasive evaluation of Crohn's disease and obscure gastrointestinal bleed. *Radiologic Clinics of North America* 2007;45(2):303-15.

Peppercorn MA. Clinical manifestations and diagnosis of Crohn's disease in adults. UptoDate online journal 2007; www.uptodate.com

Peterson K.D. Inflammatory bowel disease: impact on early teenage years. *Gastroenterology Nursing* 2008;31:235-236.

Peyrin-Biroulet L, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's Disease: Meta-analysis of placebo-controlled trials. *Clinical Gastroenterology and Hepatology* 2008;6:644-653.

Peyrin-Biroulet L., et al. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *International journal in gastroenterology* 2011;60:930-936.

Rahier JF, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *Journal of Crohn's and Colitis* 2009;3(2):47-91.

Rieder F, et al. Intestinal fibrosis in IBD—a dynamic, multifactorial process. *Nature Reviews Gastroenterology & Hepatology* 2009;6:228-235.

Rodemann JF, et al. Incidence of *Clostridium difficile* infection in inflammatopry bowel disease. *Clinical Gastroenterology & Hepatology* 2007;5:339-344.

Rosen HN. Glucocorticoids and osteoporosis: Pathogenesis and clinical features. Up to Date online journal 2007; www.uptodate.com

Rutgeerts P, et al. Biological Therapies for Inflammatory Bowel Diseases. *Gastroenterology* 2009;136:1182-1197.

Rutgeerts P, et al. What Is the Role of Endoscopy in Predicting Crohn's Disease Relapse or Course? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S183-184.

Rutgeerts PJ. The patient who fails biologic therapy: where do we go from here? www.medscape.com

Ruthruff B. Clinical review of Crohn's disease. *Journal of the American Academy of Nurse Practitioners* 2007;19(8):392-397.

Saag KG. Major side effects of glucocorticosteroids. UptoDate online journal 2007; www.uptodate.com

Sadowski D.C., et al. The use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. *The Canadian Journal of Gastroenterology* 2009;23:185-202.

Sainsbury A, et al. Review article: psychosocial factors in the quality of life of patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2005;21:499-508.

Sandborn WJ, et al. AGA Technical Review on Perianal Crohn's Disease. *Gastroenterology* 2003; 125:1508–1530.

Schaefer ME, et al. Factors that determine risk for surgery in pediatric patients with Crohn's disease. *Clinical Gastroenterology and Hepatology* 2010;8:789-794

Schmidt S., et al. Diagnostic performance of MRI for detection of intestinal fistulas in patients with complicated inflammatory bowel conditions. *European Radiology* 2007;17:2957-2963.

Schnitzler F., et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflammatory Bowel Diseases* 2011;17(9):1846-1854.

Schreiber S, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *The New England Journal of Medicine* 2007;357:239-250.

Scribano ML. Adverse effects of IBD therapies. *Inflammatory Bowel Disease* 2008;14 Suppl 2:S210-1.

Shaye OA, et al. Hepatotoxicity of 6-Mercaptopurine (6-MP) and Azathioprine (AZA) in adult IBD patients. *The American Journal of Gastroenterology* 2007;102:2488-2494.

Shen B, et al. Combined ciprofloxacin and tinidazole therapy in the treatment of chronic refractory pouchitis. *Diseases of the Colon & Rectum* 2007;50:498-508.

Siegel CA. Review article: explaining risks of inflammatory bowel disease therapy to patients. *Alimentary Pharmacology and Therapeutics* 2011;33:23-32.

Siemanowski B, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a working party of the 2005 Montreal world congress of gastroenterology. *Canadian Journal of Gastroenterology* 2005;19(Suppl A):5-36

Smillis C, et al. A meta-analysis comparing conventional end-to-end anasomosis vs. Other anastomotic configurations after resection in Crohn's disease. *Diseases of the Colon & Rectum* 2007;50:1674-1687.

Smith MA, et al. Review article: malignancy on thiopurine treatment with special reference to inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2010;32:119-130.

Sokol H, et al. Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010;59:1363-1368.

Solomkin J.S., et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2010;50:133-164.

Sousa GC, et al. A comprehensive approach to evaluate nutritional status in Crohn's patients in the era of biological therapy: A case-control study. *The American Journal of Gastroenterology* 2007 Nov;102(11):2551-2556.

Sprakes M.B., et al. Costs of care for Crohn's disease following the introduction of infliximab: A single-centre UK experience. *Alimentary Pharmacology and Therapeutics* 2010;32:1357-1363.

Steenholdt C., et al. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2011;34:51-58.

Stein J, et al. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nature Reviews Gastroenterology & Hepatology* 2010;7:599-610.

Steinhart AH, et al. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Systemic Reviews* CD 00301;2003.

Steinhart AH, Forbes A, Mills EC et al. Systematic review: the potential influence of mesalazine formulation on maintenance of remission in Crohn's disease. *Alimentary Pharmacology & Therapeutics* 2007;25:1389-1399.

Summers RW, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77 (4 Pt 2):847-869.

Surawicz C. Whats's the Best Way to Differentiate Infectious Colitis (Acute Self-Limited Colitis) from IBD? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S157-158.

Szigethy E., et al. Profile of depression in adolescents with inflammatory bowel disease; implications for treatment. *Inflammatory Bowel Diseases* 2009;15:69-74.

Taminiau JA, et al. Review article: the clinical importance of growth in children with inflammatory bowel disease: is it important to the gastroenterologist? *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:53-56.

Taxonera C., et al. Infliximab maintenance therapy is associated with decreases in direct resource use in patients with luminal or fistulizing Crohn's disease. *Journal of Clinical Gastroenterology* 2009;43:950-956.

Tilg H, et al. Gut, Inflammation and osteoporosis: basic and clinical concepts. *Gut* 2008;57:684-694.

Toruner M, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;134(4):929-936.

Tremaine WJ. Inflammatory Bowel Disease and *Clostridium difficile*—Associated Diarrhea: A growing problem. *Clinical Gastroenterology and Hepatology* 2007;5:310-311.

Turner D, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clinical Gastroenterology & Hepatology 2007;5:103-110.

Van Assche G et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *The American Journal of Gastroenterology* 2009; 98:332-339.

Van Assche G, et al. Concomitant immunosuppression does not impact on the outcome of maintenance Infliximab therapy in Crohn's Disease: Final results of the IMID trial. *Gastroenterology* 2007;132:A-103.

Van Assche G, et al. What can we expect from endoscopic dilation of the stenotic tract in Crohn's disease? *Inflammatory Bowel Disease* 2008;14 Suppl 2:S275-276.

Van Assche G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: A randomised trial. *Gastroenterology* 2008;134(7):1861-1868.

Van Langenberg D.R. and Gibson P.R. Systematic review: fatigue in inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2010;32:131-143.

Vavricka SR, et al. The Swiss IBD Cohort Study Group. Frequency and risk factors for extraintestinal manifestations in the Swiss Inflammatory Bowel Disease Cohort. *The American Journal of Gastroenterology* 2011;106:110-119.

Villanueva C. Current endoscopic therapy of variceal bleeding. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):261-278.

Vogelsang H. Do Changes in Intestinal Permeability Predict Disease Relapse in Crohn's Disease? *Inflammatory Bowel Disease* 2008; 14 Suppl 2:S162-163.

Walker J.R., et al. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *The American Journal of Gastroenterology* 2008;103:1989-97.

Walker MM, et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. *Gastroenterology* 2010;139:112-9.

Walters TD, et al. Mechanisms of growth impairment in pediatric Crohn's disease. *Gastroenterology and Hepatology* 2009; 6:513.

Waugh AWG, et al. Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long term follow up of a single centre cohort. *Alimentary Pharmacology and Therapeutics* 2010;32:1129-1134.

Weersma RK, et al. Inflammatory bowel disease and genetics. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:57-65.

Wibmer AG, et al.. Comparison of strictureplasty and endoscopic balloon dilatation for structuring Crohn's disease-review of the literature. *International Journal of Colorectal Disease* 2010;25(10):1149-1157.

Wiese D.M., et al. The effects of an oral supplement enriched with fish oil, probiotics, and antioxidants on nutrition status in Crohn's disease patients. *Nutrition in Clinical Practice* 2011;26:463-473.

Wikipedia contributors. Crohn's Disease. Wikipedia, the free encyclopedia. August 16, 2009 at 23:24. Available at http://en.wikipedia.org/wiki/Crohn%27s_disease.

William C. What Is the Optimal Interval of Surveillance Colonoscopy in Patients with Long-standing Ulcerative Colitis? *Inflammatory Bowel Disease* 2008; 14 Suppl 2:S194-195.

Willing BP, et al. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. *Gastroenterology* 2010 Dec;139(6):1844-1854.

Xavier RJ, et al. Autophagy as an important process in gut homeostasis and Crohn's disease pathogenesis. *Gut* 2008;57(6):717-20.

Xavier, R, et al. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;448(7152):427-434.

Yantiss RK, et al. Pitfalls in the interpretation of non-neoplastic mucosal biopsies in Inflammatory bowel disease. *The American Journal of Gastroenterology* 2007;102(4):890-904.

Ziech M, et al. Imaging of Perianal Fistulas. *Clinical Gastroenterology and Hepatology* 2009;7:1037-1045.

➢ *Infection*

Hasnain, S.Z., et al. Muc5ac: a critical component mediating the rejection of enteric nematodes. *Journal of Experimental Medicine.* 2011; 208(5): 893-900.

➢ *Motility*

Margolis K., et al. Enteric neuronal density contributes to the severity of intestinal inflammation *Gastroenterology* 2011;141:588-598.

➢ *Miscellaneous*

Auerbach M. and Ballard H. Clinical use of intravenous iron: administration, efficacy and safety. *Hematology American Society of Hematology Education Program* 2010:338-347.

Dongmei Ye, et al. MicroRNA Regulation of Intestinal Epithelial Tight Junction Permeability. *Gastroenterology* 2011;141:1323-1333.

Ippolito D., et al. MR enterography with polyethylene glycol as oral contrast medium in the follow-up of patients with Crohn disease: comparison with CT enterography. *Abdominal Imaging* 2010;35:563-570.

Nicklas TA, et al. Self-perceived lactose intolerance results in lower intakes of calcium and dairy foods and is associated with hypertension and diabetes in adults. *American Journal of Clinical Nutrition.* 2011;94(1):191-8.

Rey J.F., et al. Optimal preparation for small bowel examinations with video capsule endoscopy. *Digestive and Liver Disease* 2009;41:486-493.

Scheirey C.D., et al. Angio-tensin-converting enzyme inhibitor-induced small-bowel angioedema: clinical and imaging finding in 20 patients *American Journal of Roentgenology* 2011;197:393-398.

COLON

➢ *Bleeding*

American Gastroenterological Association Medical Position Statement: guidelines on intestinal ischemia. *Gastroenterology* 2000;118:951-953.

Ashraf M, et al. Ischemic colitis with atypical reactive changes that mimic dysplasia (pseudodysplasia). *Archives of Pathology & Laboratory Medicine* 2001;125:224.

Brandt L. Intestinal ischemia. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:2563-2583.

Brandt LJ, et al. AGA technical review on intestinal ischemia. *Gastroenterology* 2000;118:954-968.

Brandt LJ, et al. Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: A study of 313 cases supported by histology. *The American Journal of Gastroenterology* 2010;105:2245-2252.

Cooperman A. Diverticulitis. *eMedicine online* journal 2006; www.emedicine.com

Ferzoco LB, et al. Acute diverticulitis. *The New England Journal of Medicine* 1998;338(21):1521-1525.

Goldberg MB. Infections due to enteric pathogens Campylobacter, Salmonella, Shigella, Yersinia, Vibrio and Helicobacter. In: Scientific American Medicine. New York: Scientific American, 2002.

Goldstein NS, et al. Crohn's-like complications in patients with ulcerative colitis after total proctocolectomy and ileal pouch-anal anastomosis. *The American Journal of Surgical Pathology* 1997; 21:1343-1353.

Griffiths JK, et al. Other bacterial diarrhoeas. *Bailliere's Clinical Gastroenterology* 1993; 7:263-305.

Hogenauer C, *et al.* Klebsiella oxytoca as a causative organism of antibiotic-associated hemorrhagic colitis. *The New England Journal of Medicine* 2006;355:2418-2426.

Jensen DM, et al. Diagnosis and treatment of severe hematochezia. *Gastroenterology* 1988; 95:1569–1574.

Khan AN. Ischemic Colitis. *Emedicine Online Journal.*http://emedicine.medscape.com/article/366808-overview.

Konvolinka CW. Acute diverticulitis under age forty. *American Journal of Surgery* 1994; 167:562–565.

Kozuch PL, et al. Review article: diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. *Alimentary Pharmacology and Therapeutics* 2005;21:201–215.

Leddin D, et al. Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: Guidelines on colon cancer screening. *Canadian Journal Gastroenterology* 2004; 18:93-99.

Legace-Wiens PR, et al. Dientamoeba fragilis: an emerging role in intestinal disease. *Canadian Medical Association Journal* 2006;175:468-469.

Levin B. Colorectal Cancer. In: Scientific American Medicine. New York: Scientific American, 2002.

Longstreth GF, et al. Epidemiology, Clinical Features, High-Risk Factors, and Outcome of Acute Large Bowel Ischemia. *Clinical Gastroenterology & Hepatology* 2009; 7:1075-1080.

Phillips SF, Pemberton JH, Shorter RG (eds.). The large intestine: physiology, pathophysiology and disease. New York: Raven Press, 1991.

Quinolones in acute non-travellers' diarrhoea [Editorial]. *Lancet* 1991; 335:282.

Regula J, et al. Vascular lesions of the gastrointestinal tract. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):313-328.

Reinus JF, Brandt LJ. Vascular ectasias and diverticulosis. *Gastroenterology Clinics of North America* 1994; 23:1–20.

Sheth AA, et al. Diverticular disease and diverticulitis. *American Journal of Gastroenterology* 2008;103:1550-1556.

Sreenarasimhaiah J, et al. Chronic mesenteric ischemia. *Best Practice & Research Clinical Gastroenterology* 2005;19(2):283-295.

Stollman N, et al. Diverticular disease of the colon. *The Lancet* 2004;363(9409):631-9.

Tursi A, et al. Inflammatory manifestations at colonoscopy in patients with colonic diverticular disease. *Alimentary Pharmacology and Therapeutics* 2011;33:358-365.

Wikipedia Contributors. Ischemic Colitis. *Wikipedia, the online encyclopedia*. 2009 at 00:27. Available at http://en.wikipedia.org/wiki/Ischemic_colitis.

➢ *Ulcerative Colitis*

Bartlett JG. Antibiotic-associated diarrhea. *The New England Journal of Medicine* 2002; 346(5): 334-339.

Chande, N. Microscopic colitis: an approach to treatment. *Canadian Journal of Gastroenterology* 2008;22:686-688.

Coffey JC, et al. Pathoenesis of and unifying hypotesis for idiopathic pouchitis. *The American Journal of Gastroenterology* 2009;104:1013-1023.

Colombel, J. F., et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology.* 2011; 141(4): 1194-1201.

De Silva PSA, et al. An association between dietary arachidonic acid, measured in adipose tissue and ulcerative colitis. *Gastroenterology* 2010;139:1912-1917.

Fernandez-Banares F, et al. Collagenous and Lymphocytic Colitis: Evaluation of Clinical and Histological Features, Response to Treatment, and Long-Term Follow-Up. *The American Journal of Gastroenterology* 2003; 98:340.

Fleshner P, et al. Both preoperative perinuclear antineutrophil cytoplasmic antibody and anti CBir1 expression in ulcerative colitis patients influence pouchitis development after ileal pouch-anal anastomosis. *Clinical Gastroenterology and Hepatology* 2008;6:561-8.

Freeman HJ. Limitations in assessment of mucosal healing in inflammatory bowel disease. *World Journal of Gastroenterology* 2010;16(1):15-20.

Freeman HJ. Surveillance for colitis-associated colon neoplasia. *World Journal of Gastroenterology* 2010;16(37):4646-4651.

Giannella RA. Infectious enteritis and proctocolitis and bacterial food poisoning. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/ Management* 2006:2334-2382.

Gionchetti Paolo, et al. Management of pouch dysfunction or pouchitis with an ileoanal pouch. *Best Practice & Research Clinical Gastroenterology* 2004;18(5):993-1006.

Goldstein NS, et al. Crohn's colitis-like change in sigmoid diverticulitis specimens is usually an idiosyncratic inflammatory response to the diverticulosis rather than Crohn's colitis. *The American Journal of Surgical Pathology* 2000; 24:668-675.

Hawthorne AB, et al. Review article: medication non-adherence in ulcerative colitis – strategies to improve adherence with mesalazine and other maintenance therapies. *Alimentary Pharmacology and Therapeutics* 2008;27:1157-1166.

Innis SM, et al. Perinatal lipid nutrition alters early intestinal development and programs the response to experimental colitis in young adult rats. Nutrition and Metabolism Research Program, Child and Family Research Institute, and Division of Gastroenterology, Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada

Kane SV, et al. Review article: understanding adherence to medication in ulcerative colitis- innovative thinking and evolving concepts. *Alimentary Pharmacology and Therapeutics* 2010;32:1051-1058.

Keszthelyi D, et al. Proton pump inhibitor use is associated with an increased risk for microscopic colitis: a case-control study. *Alimentary Pharmacology and Therapeutics* 2010;32:1124-1128.

Kornbluth A, et al. Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee. *The American Journal of Gastroenterology* 2004;99:1371-1385.

Kruis W, et al. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2011; 33(3):313-22.

Kuehne SA, et al. The role of toxin A and toxin B in *Clostridium difficile*infection. *Nature* 2010;4677:11-713.

Nyhlin N, et al. Systematic review: microscopic colitis. *Alimentary Pharmacology and Therapeutics* 2006;23:1525–1534.

Oussalah A, et al. A Multicenter Experience With Infliximab for Ulcerative Colitis: Outcomes and Predictors of Response, Optimization, Colectomy, and Hospitalization. *The American Journal of Gastroenterology* 2010;105:2617-2625.

Pardi DS, et al. Lymphocytic Colitis: Clinical Features, Treatment, and Outcomes. *The American Journal of Gastroenterology* 2002;97:2829–2833.

Sartor RB, SandbornWJ (eds). Kirsner's Inflammatory Bowel Diseases 6th edition. Saunders, 2004.

Sherlock M.E., et al. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2010:CD007698.

Su, Chinyu, et al. Ulcerative colitis. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2006*:*2499-2538.

Subramanian, V., et al. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics.* 2011; 33(3): 304–312.

Taxonera C, et al. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. *Alimentary Pharmacology and Therapeutics* 2011;33:340-348.

Thanaraj S, et al. Systematic review: granulocyte/monocyte adsorptive apheresis for ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2010;32:1297-1306.

Tursi A, et al. A. Treatment of Relapsing Mild-to-Moderate Ulcerative Colitis With the Probiotic VSL#3 as Adjunctive to a Standard Pharmaceutical Treatment: A Double-Blind, Randomized, Placebo-Controlled Study. *The American Journal of Gastroenterology* 2010;105:2218-2227.

Velayos FS, et al. Effect of 5 aminosalicy late use on cancer and dysplasia risk: A systematic review and meta analysis of observational studies. *The American Journal of Gastroenterology* 2005; 100:1345-1353.

Velayos FS, et al. Prevalence of Colorectal Cancer Surveillance for Ulcerative Colitis in an Integrated Health Care Delivery System. *Gastroenterology* 2010;139:1511-1518.

Wilcox, C. Mel. Gastrointestinal consequences of infection with human immunodeficiency virus. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/ Management* 2006:668-679.

Wolf JM, et al. The impact of ursodeoxycholic acid on cancer, dysplasia, and mortality in ulcerative colitis patients with primary sclerosing cholangitis. *Alimentary Pharmacology and Therapeutics* 2005;22:783-788.

➤ *Neoplasia*

Achkar E, et al. Colorectal cancer screening with fecal occult blood testing (FOBT): an international perspective. *The American Journal of Gastroenterology* 2006;101(2):212.

Ahnen DJ, et al. Approach to the patient with colonic polyps. *UpToDate online journal.* www.uptodate.com

Almansa C., et al. Association between visual gaze patterns and adenoma detection rate during colonoscopy: a preliminary investigation. *The American Journal of Gastroenterology* 2011;106:1070-1074.

Aminalai A., et al. Live image processing does not increase adenoma detection rate during colonoscopy: a randomized comparison between FICE and conventional imaging (Berlin Colonoscopy Project 5, BECOP-5). *The American Journal of Gastroenterology* 2010;105:2383-2388.

Anke M. Leufkens, et al. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointestinal Endoscopy* 2011;73:480-489.

Arber N, et al. Chemoprevention of colorectal neoplasia: the potential for personalized medicine. *Gastroenterology* 2008;134(4):1224-1237.

Armstrong D, et al. Canadian credentialing guidelines for endoscopic privileges: An Overview. *The Canadian Journal of Gastroenterology* 2007;21(12):797-801.

Armstrong D, et al. Point of care, peer comparator colonoscopy practice audit: The Canadian Association of Gastroenterology quality program- endoscopy. *The Canadian Journal of Gastroenterology* 2011;25:13-20.

ASGE guideline: colorectal cancer screening and surveillance. *Gastrointestinal Endoscopy* 2006; 63(4):546-557.

Atkin WS, et al. (Department of Surgery and Cancer, Imperial College of London, St. Mary's Campus, UK). Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multi-centre randomised controlled trial. *The Lancet* 2010;375:1624-1633.

Augsten M., et al. A digest on the role of the tumor microenvironment in gastrointestinal cancers. *Cancer Microenvironment* 2010;3:167-176.

Aune D., et al. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. *Gastroenterology* 2011;141:106-118.

Baca B., et al. Surveillance after colorectal cancer resection: a systematic review. *Diseases of the Colon and Rectum* 2011;54:1036-1048.

Backman V. and Roy H.K. Light-scattering technologies for field carcinogenesis detection: a modality for endoscopic prescreening. *Gastroenterology* 2011;140:35-41.

Bardelli A. and Siena S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. *Journal of Clinical Oncology* 2010;28:1254-1261.

Baron TH, et al. Endoscopic stenting of colonic tumours. *Best Practice & Research Clinical Gastroenterology* 2004;18(1):209-229.

Baxter NN, et al. Association of colonoscopy and death from colorectal cancer. *Annals of Internal Medicine* 2009;150:1-8.

Bellam N. and Pasche B. Tgf-beta signaling alterations and colon cancer. *Cancer Treatment and Research* 2010;155:85-103.

Belsey J, et al. Systematic review: oral bowel preparation for colonoscopy. *Alimentary Pharmacology and Therapeutics* 2007;25(4):373-84.

Benson M, et al. A Comparison of Optical Colonoscopy and CT Colonography Screening Strategies in the Detection and Recovery of Subcentimeter Adenomas. *The American Journal of Gastroenterology* 2010;105:2578-2585.

Bonadona V., et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *Journal of the American Medical Association* 2011;305:2304-2310.

Bond JH, et al. The place of fecal occult blood test in colorectal cancer screening in 2006: The U.S. perspective. *The American Journal of Gastroenterology* 2006;101:219-2212.

Boparai KS, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. *Gut* 2010;59:1094-1100.

Botma A., et al. Body mass index increases risk of colorectal adenomas in men with Lynch syndrome: the GEOLynch cohort study. *Journal of Clinical Oncology* 2010;28:4346-4353.

Brenner H, et al. Protection from colorectal cancer after colonoscopy. *Annals of Internal Medicine* 2011;154:22-30.

Brenner H., et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *Journal of the National Cancer Institute* 2010;102:89-98.

Bretthauer M. Evidence for colorectal cancer screening. *Best practice and research clinical gastroenterology* 2010;24:417-425.

Brown S. R, and Baraza, W. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *Cochrane Database of Systematic Reviews*. 2010; 10. Art. No.: CD006439. DOI: 10.1002/14651858.CD006439.pub3.

Buchner A.M., et al. High-definition colonoscopy detects colorectal polyps at a higher rate than standard white-light colonoscopy. *Clinical Gastroenterology and Hepatology* 2010;8:364-370.

Buddingh K.T., et al. Locaion in the right hemi-colon is an independent risk factor for delayed post-polypectomy hemorrhage: a multi-center case-control study. *The American Journal of Gastroenterology* 2011;106:1119-1124.

Burke C.A., et al. A comparison of high-definition versus conventional colonoscopies for polyp detection. *Digestive Diseases and Sciences* 2010;55:1716-1720.

Burt R, et al. Genetic testing for inherited colon cancer. *Gastroenterology* 2005;128:1696-1716.

Cappell MS (ed). Colon Cancer Screening, Surveillance, Prevention and Therapy. Gastroenterology Clinics of North America 2008; 31(1).

Chaput, U., et al. Risk factors for advanced adenomas amongst small and diminutive colorectal polyps: A prospective monocenter study. *Digestive and Liver Disease*. 2011; 43(8): 609-612.

Chung DC, et al. Cellular growth and neoplasia. *Sleisenger & Fordtran's gastrointestinal and liver disease:Pathophysiology/Diagnosis/Management* 2006: 67-82.

Chung S.J., et al. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointestinal Endoscopy* 2010;72:136-142.

Cole B.F., et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *Journal of the National Cancer institute* 2009;101:256-266.

Corporaal S., et al. Low-volume PEG plus ascorbic acid versus high-volume PEG as bowel preparation for colonoscopy. *Scandinavian Journal of Gastroenterology* 2010;45:1380-1386.

Dahabreh IJ, et al. Systematic review: Anti epidermal growth factor receptor treatment effect modication by KRAS mutations in advanced colorectal cancer. *Annals of Internal Medicine* 2011;154:37-49.

Dahm C.C., et al. Dietary fiber and colorectal cancer risk: a nested case-control study using food diaries. *Journal of National Cancer Institute* 2010;102:614-626.

Dahm C.C., et al. Dietary fiber and colorectal cancer risk: a nested case-control study using food diaries. *American Journal of Clinical Nutrition* 2010;92:1429-1435.

David G Pfister, et al. Surveillance strategies after curative treatment of colorectal cancer. *The New England Journal of Medicine* 2004; 350:2357-82.

Day L.W., et al. Colorectal cancer screening and surveillance in the elderly patient. *The American Journal of Gastroenterology* 2011;106:1197-1206.

DeMarco D.C., et al. Impact of experience with a retrograde-viewing device on adenoma detection rates and withdrawal times during colonoscopy: The Third Eye Retroscope study group. *Gastrointestinal Endoscopy* 2010;71:542-550.

Dong, M., et al. Missed work related to mid-week screening colonoscopy. *Digestive Diseases and Sciences*. 2011; 56(7): 2114-2119.

East J.E., et al. Dynamic patient position changes during colonoscope withdrawal increase adenoma detection: a randomized, crossover trail. *Gastrointestinal Endoscopy* 2011;73:456-463.
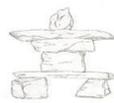
East JE, et al. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. *Gastroenterology Clinics of North America*.2008;37:25-46.

Efthymiou M., et al. Biopsy forceps is inadequate for the resection of diminutive polyps. *Endoscopy* 2011;43:312-316.

Elsen GM. Screening for colorectal cancer in patients with a First-Degree relative with colonic neoplasia. *Annals of Internal Medicine* 2005;143:190-198.

Fornaro L., et al. Palliative treatment of unresectable metastatic colorectal cancer. *Expert Opinion on Pharmacotherapy* 2010;11:63-77.

Fung T.T. The Mediterranean and Dietary Approaches to Stop Hypertension(DASH) diets and colorectal cancer. *American Journal of Clinical Nutrition* 2010;92:1429-1435.

Galliatsatos P, et al. Familial adenomatous polyposis. *The American Journal of Gastroenterology* 2006;101:385-398.

Ghosh S, et al. Practice audit in gastroenterology- the route to improving quality and safely. *The Canadian Journal of Gastroenterology* 2011;25:12

Giardiello FM, et al. Peutz-Jeghers syndrome and management recommendations. *Clinical Gastroenterology and Hepatology* 2006;4:408-415.

Glynne-Jones R, et al. Multimodal treatment of rectal cancer. *Best Practice & Research Clinical Gastroenterology* 2007;21(6):1049-1070.

Goetz M, et al. In vivo molecular imaging of colorectal cancer with confocal endomicroscopy by targeting epidermal growth factor receptor. *Gastroenterology*. 2010;138(2):435-46.

Goodman A. Minorities benefit from more sophisticated colon cancer screening. *Oncology News International* 2010;19:7.

Grothey A. EGFR antibodies in colorectal cancer: where do they belong? *Journal of Clinical Oncology* 2010;28:4668-4670.

Gurudu SR, et al. Sessile serrated adenomas: demographic, endoscopic and pathological characteristics. *World Journal of Gastroenterology* 2010;16:3402-3405.

Gustafsson U.O., et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Archives of Surgery* 2011;146:571-577.

Hassan C, et al. Performance improvements of imaging based screening tests. *Best practice and research clinical gastroenterology* 2010;24:493-507.

Hazewinkel, Y. and Dekker, E. Colonoscopy: basic principles and novel techniques. *Nature Reviews Gastroenterology and Hepatology*. 2011; 8: 554-564.

Heresbach D., et al. A national survey of endoscopic mucosal resection for superficial gastrointestinal neoplasia. *Endoscopy* 2010;42:806-813.

Hewett D.G. and Rex D. K. Colonoscopy and diminutive polyps: hot or cold biopsy or snare? Do I send to pathology? *Clinical Gastroenterology and Hepatology* 2011;9:102-105.

Hiraoka S, et al. The Presence of Large Serrated Polyps Increases Risk for Colorectal Cancer. *Gastroenterology* 2010;139:1503-1510.

Hlavaty T., et al. Colorectal cancer screening in patients with ulcerative and crohn's colitis with use of colonoscopy, chromoendoscopy and confocal endomicroscopy. *European Journal of Gastroenterology & Hepatology* 2011;23:680-689.

Hoffman A., et al. High definition colonoscopy combined with i-Scan is superior in the detection of colorectal neoplasias compared with standard video colonoscopy: a prospective randomized controlled trial. *Endoscopy* 2010;42:827-833.

Hoffmeister M, et al. Male Sex and Smoking Have a Larger Impact on the Prevalence of Colorectal Neoplasia Than Family History of Colorectal Cancer. *Clinical Gastroenterology and Hepatology* 2010;8:870-876.

Hundt S, et al. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. *Annals of Internal Medicine* 2009;150:162-169.

Ignjatovic A., et al. What is the most reliable imaging modality for small colonic polyp characterization? Study of white-light. Autofluorescence, narrow-band imaging. *Endoscopy* 2011;43:94-99.

Imperiale TF, et al. Results of screening colonoscopy among persons 40 to 49 years of age. *The New England Journal of Medicine* 2002;346(23):1781-1785.

Inadomi J. Interval Cancers After Colonoscopy: The Importance of Training. *The American Journal of Gastroenterology* 2010;105:2597-2598.

Itzkowitz, et al. Colonic polyps and polyposis syndromes. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:2743-2747.

Ivan Jovanovic, et al. The Submucosal Cushion Does Not Improve the Histologic Evalutaion of Adenomatous Colon Polyps Resected by Snare Polypectomy. *Clinical Gastroenterology and Hepatology* 2011;9:910-913.

Jass JR, et al. Colorectal polyposes: From phenotype to diagnosis. *Pathology, Research and Practice* 2008;204:431-447.

Jenab M. et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations: A nested case-control study. *British Medical Journal* 2010 Jan 21;340:b5500.

Jiang Y, et al. Assessment of K-ras mutation: A step toward personalized medicine for patients with colorectal cancer. *Cancer.* 2009;115(16):3609-3617.

Johnson CC, et al. Nonsteroidal anti-inflammatory Drug Use and Colorectal Polyps in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *The American Journal of Gastroenterology* 2010;10:2646-2655.

Johnson CD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *The New England Journal of Medicine*. 2008 Sep 18;359(12):1207-1217.

Johnson IT, et al. Nutrition, obesity and colorectal cancer. *Alimentary Pharmacology and Therapeutics* 2007;26(2):161-181.

Jovanovic I., et al. The submucosal cushion does not improve the histologic evaluation of adenomatous colon polyps resected by snare polypectomy. *Clinical Gastroenterology and Hepatology* 2011;9:910-913.

Kahi C.J., et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *Clinical Gastroenterology and Hepatology* 2011;9:42-46.

Kahi CJ, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *Clinical Gastroenterology and Hepatology* 2011;9:42-46.

Kaminski M.F., et al. Quality indicators for colonoscopy and the risk of interval cancer. *The New England Journal of Medicine* 2010;362:1795-1803.

Keswani R.N. Single-ballon colonoscopy versus repeat standard colonoscopy for previous incomplete colonoscopy: a randomized, controlled trial. *Gastrointestinal Endoscopy* 2011;73:507-512.

Kilgore T.W., et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointestinal Endoscopy* 2011;73:1240-1245.

Kirkegaard H, et al. Association of adherence to life style recommendations and risk of colorectal cancer: A prospective Danish cohort study. *British Medical Journal* 2010;341:c5504

Ko C.W., et al. Serious complications within 30 days of screeing and surveillance colonoscopy are uncommon. *Clinical Gastroenterology and Hepatology* 2010;8:166-173.

Kourkalis G, et al. Hereditary nonpolyposis colorectal cancer (Lynch Syndrome): criteria for identification and management. *Digestive Diseases and Sciences* 2005;50(2):336-344.

Kuiper T., et al. Endoscopic trimodal imaging detects colonic neoplasia as well as standard video enscopy. *Gastroenterology* 2011;140:1887-1894.

Laiyemo A.O., et al. Likelihood of missed and recurrent adenomas in the proximal versus the distal colon. *Gastrointestinal Endoscopy* 2011;74:253-261.
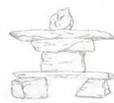
Laiyemo A.O., et al. Race and colorectal cancer disparities: health-care utilization vs different cancer susceptibilities. *Journal of National Cancer Institute* 2010:102:538-546.

Lane JM, et al. Interval fecal immunochemical testing in a colonoscopic surveillance program speeds detection of colorectal neoplasia. *Gastroenterology* 2010;139:1918-1926.

Lansdorp-Vogelaar I, et al. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. *Annals of Internal Medicine*. 2010;153:368-377.

Lashner BA. Colon cancer in IBD: what's the latest on screening, surveillance and treatment? *ACG Annual Postgraduate Course*2009:149-152.

Lawrance I.C., et al. Bowel cleansing for colonoscopy: prospective randomized assessment of efficacy and of induced mucosal abnormality with three preparation agents. *Endoscopy* 2011;43:412-418.

Leddin D, et al. Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: Guidelines on colon cancer screening. *The Canadian Journal of Gastroenterology* 2004;18(2): 93-99.

Lee J.M., et al. Effects of hyosine N.-butyl bromide on the detection of polyps during colonoscopy. *Hepatogastroenterology* 2010;57:90-94.

Leufkens A.M., et al. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointestinal Endoscopy* 2011;73:480-489.

Levin B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force in Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134(5):1570-95.

Levine JS, et al. Adenomatous polyps of the colon. *The New England Journal of Medicine* 2006;355:2551-2557.

Lieberman DA, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *The New England Journal of Medicine* 2000; 343(3):162-168.

Lieberman DA, et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology* 2007;133:1077-1085.

Liu Z, et al. Randomised clinical trial: the effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery – a double-blind study. *Alimentary Pharmacology and Therapeutics* 2011;33:50-63.

Lynch HT, et al. Hereditary Colorectal Cancer. *The New England Journal of Medicine* 2003;348:919-932.

Mannath J., et al.Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. *Digestive Diseases and Sciences* 2011;56:2389-2395.

Mariani P., et al. Concordant analysis of KRAS status in primary colon carcinoma and matched metastasis. *Anticancer Research* 2010;30:4229-4233.

Marmo R., et al. Effective bowel cleansing before colonoscopy: a randomized study of split-dosage versus non-split dosage regimens of high-volume versus low-volume polyethylene glycol solutions. *Gastrointestinal Endoscopy* 2010;72:313-320.

Martinez ME, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology* 2009;136:832-41.

McCutchen A.S., et al. Lower albumin levels in African Americans at colon cancer diagnosis; a potential explanation for outcome disparities between groups? *International Journal of Colorectal Disease* 2011;26:469-472.

Melton SD, et al. Biomarkers and molecular diagnosis of gastrointestinal and pancreatic neoplasms. *Nature Reviews Gastroenterology & Hepatology* 2010;7:620-628.

Misra T, et al. Endoscopic perforation rates at a Canadian university teaching hospital. *The Canadian Journal of Gastroenterology* 2004;18(4):221-227.

Moss A., et al. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyp of the colon. *The American Journal of Gastroenterology* 2010;105:2375-2382.

Moss A., et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011;140:1909-1918.

Neerincx M., et al. Colonic work-up after incomplete colonoscopy: significant new findings during follow-up. *Endoscopy* 2010;42:730-735.

Newmark H.L., et al. A Western-style diet induces benign and malignant neoplasms in the colon of normal C57BI/6 mice. *Carcinogenesis* 2011;22:1871-1875.

Niimi K., et al. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2010;42:723-729.

Nyberg C, et al. The safety of osmotically acting cathartics in colonic cleansing. *Nature Reviews Gastroenterology & Hepatology* 2010;7:557-564.

Nyberg C, et al. Adverse events associated with use of the three major types of osmotically acting cathartics. *Nature Reviews Gastroenterology and hepatology* 2010;7:558.

Nyberg C, et al. Risk factors for acute phosphate nephropathy. *Nature Reviews Gastroenterology and hepatology* 2010;7:559.

Ollberding N.J., et al. Racial/ethnic differences in colorectal cancer risk: the multiethnic cohort study. *International Journal of Cancer* 2011 March 25.

Pan M.H., et al. Molecular mechanisms for chemoprevention of colorectal cancer by natural dietary compounds. *Molecular Nutrition Food and Research* 2011;55:32-45.

Pander J., et al. Correlation of FCGR3A and EGFR germline polymorphisms with the efficacy of cetuximab in KRAS wild-type metastatic colorectal cancer. *European Journal of Cancer*. 2010;46:1829-1834.

Parsche B., et al. Constitutively decreased TGFBR1 allelic expression is a common finding in colorectal cancer and is associated with three TGFBR1 SNPs. *Journal of Experimental and Clinical Cancer Research* 2010;29:57.

Pickhardt PJ, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *The New England Journal of Medicine* 2003;349:2191-2200.

Pohl H, et al. Colorectal cancers detected after colonoscopy frequently result from missed lesions. *Clinical Gastroenterology and hepatology* 2010;8:858-864.

Pohl J., et al. Pancolonic chromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: a randomized two-centre trial. *International journal in gastroenterology* 2011;60:485-490.

Rabeneck L, et al. Association between colonoscopy rates and colorectal cancer mortality. *The American Journal of Gastroenterology* 2010;105:1627.

Radaelli F., et al. Warm water infusion versus air insufflation for unsedated colonoscopy: a randomized controlled trial. *Gastrointestinal Endoscopy* 2011;72:701-709.

Ramsoekh D., et al. A back-to-back comparison of white light video endoscopy with autofluorescence endoscopy for adenoma detection in high-risk subjects. *International journal in gastroenterology* 2010;59:785-793.

Rao SSC (ed). Disorders of the Pelvic Floor and Anorectum. Gastroenterol Clin North Am 2008;37(3).

Regula J, et al. Targeting risk groups for screening. *Best practice and research clinical gastroenterology* 2010;24:407-416.

Rex DK, et al. ACG colorectal cancer prevention action plan: update on CT-colonography. *The American Journal of Gastroenterology* 2006;101:1410-1413.

Rex DK, et al. American College of Gastroenterology Action Plan for Colorectal Cancer Prevention. *The American Journal of Gastroenterology* 2004;99(4):574-7.

Rex DK, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. *The American Journal of Gastroenterology* 2009;104:739-750.

Rex DK, et al. Guidelines for colonoscopy surveillance after cancer resection: A consensus update by the American Cancer Society and the U.S Multi Society Task Force on Colorectal Cancer. *Gastroenterology* 2006;130:1865-1871.

Rex, Douglas K. Screening and surveillance for colorectal cancer. *ACG Annual Postgraduate course book 2008*:89-91.

Ricci-Vitani L, et al. Colon Cancer stem cells. *Gut* 2008;57(4):538-548.

Risio M. Reprint of : The natural history of adenomas. *Best practice and research clinical gastroenterology* 2010;24:397-406.

Rothwell P.M., et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomized trials. *Lancet* 2010;376:1741-1750.

Rotondano G., et al. Endocytoscopic classification of preneoplastic lesions in the colorectum. *International Journal of Colorectal Disease* 2010;25:1111-1116.

Roy H.K., et al. Colonoscopy and optical biopsy: bridging technological advances to clinical practice. *Gastroenterology* 2011;140:1863-1867.

Saito Y., et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointestinal Endoscopy* 2010;72:1217-1225.

Sandler RS. Colonoscopy and colorectal cancer mortality: Strong beliefs or strong facts? *The American Journal of Gastroenterology* 2010;105:1633.

Sanduleanu S., et al. In vivo diagnosis and classification of colorectal neoplasia by chromoendoscopy-guided confocal laser endomicroscopy. *Clinical Gastroenterology and Hepatology* 2010;8:371-378.

Sauk, J., et al. High-definition and filter-aided colonoscopy. *Gastroenterology Clinics of North America*. 2010; 39(4): 859-881.

Schreiner MA, et al. Proximal and Large Hyperplastic and Nondysplastic Serrated Polyps Detected by Colonoscopy Are Associated With Neoplasia. *Gastroenterology* 2010;139:1497-1502.

Schulmann K, et al. The patient with multiple intestinal polyps. *Best Practice & Research Clinical Gastroenterology* 2007;21(3):409-426.

Sheth RA, et al. Optical molecular imaging and its emerging role in colorectal cancer. *American Journal of Physiology Gastrointestinal and Liver Physiology* 2010;299:G807-G820.

Singh H, et al. Rate and Predictors of Early/Missed Colorectal Cancers After Colonoscopy in Manitoba: A Population-Based Study. *The American Journal of Gastroenterology* 2010;105:2588-2596.

Singh H, et al. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010;139:1128-1137.

Spiegel B.M., et al. Development and validation of a novel patient educational booklet to enhance colonoscopy preparation. *The American Journal of Gastroenterology* 2011;106:875-883.

Stallmach A., et al. An unmet medical need: advances in endoscopic imaging of colorectal neoplasia. *Journal of Biophotonics* 2011;4:482-489.

Steckelberg A., et al. Effect of evidence based risk information on "informed choice" in colorectal cancer screening: randomized controlled trial. *British Medical Journal* 2011;342:d3193.

Stevens T, et al. Colonoscopy screening in the elderly: when to stop? *The American Journal of Gastroenterology* 2003;98(8): 1881-1885.

Stoffel EM, et al. Genetic Testing for Hereditary Colorectal Cancer: Challenges in Identifying, Counseling, and Managing High-Risk Patients. *Gastroenterology* 2010;139:1436-1443.

Suak J., et al. High-definition and filter-aided colonoscopy. *Gastroenterology Clinics of North America* 2010;39:859-881.

Subramanian V, et al. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy*. 2011; 43: 499-505.

Subramanian V., et al. Meta-analysisL the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2011;33:304-312.

Tee H.P., et al. Prospective randomized controlled trial evaluating cap-assisted colonoscopy vs standard colonoscopy. *World Journal of Gastroenterology* 2010;16:3905-3910.

Tejpar, Sabine, et al. The use of molecular markers in the diagnosis and treatment of colorectal cancer. *Best Practice & Research Clinical Gastroenterology* 2007;21(6):1071-1087.

Thackeray EW, et al. Colon neoplasms develop early in the course of inflammatory bowel disease and primary sclerosing cholangitis. *Clinical gastroenterology and hepatology* 2011;9:52-56.

Tribonias G., et al. Comparison of standard vs. high-definition, wide-angle colonoscopy for polyp detection: a randomized controlled trial. *Colorectal Disease* 2010;12:e260-e266.

U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine* 2008;149:627-37.

UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomized trial. *The Lancet* 2002;359:1291-3000.

Van Bree., et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. *Gastroenterology* 2011;141(3):872-880.

Van Dam L, et al. Performance improvements of stool based screening tests. *Best practice and research clinical gastroenterology* 2010;24:479-492.

Van Den Broek FJ, et al. New developments in colonic imaging. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:91-9.

Vasen HFA, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. *Gastroenterology* 2010;138:2300.

Vasen HFA, et al. Review article: the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *Alimentary Pharmacology and Therapeutics* 2007;26 (Suppl 2):113-126.

Velayos FS, et al. Predictive and Protective factors associated with colorectal cancer in ulcerative colitis: A Case-control study. *Gastroenterology* 2006;130:1941-1949.

Wallace M.B. and Kiesslich R. Advances in endoscopic imaging of colorectal neoplasia. *Gastroenterology* 2010;138:2140-2150.

Wallace M.B., et al. The safety of intravenous fluorescein for confocal laser endomicroscopy in the gastrointestinal tract. *Alimentary Pharmacology and Therapeutics* 2010;31:548-552.

Walsh JME, et al. Colorectal cancer screening: scientific review. *The Journal of the American Medical Association* 2003;289(10):1288-1296.

Waye J.D. Wide view and retroview during colonoscopy. *Gastroenterology Clinics of North America* 2010;39:883-900.

Waye J.D., et al. A retrograde-viewing device improves detection of adenomas in the colon: a prospective efficacy evaluation. *Gastrointestinal Endoscopy* 2010;71:551-556.

West N.J., et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *International journal in gastroenterology* 2010;59:918-925.

West NJ, et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 2010;59:918.

Whynes DK, et al. Analysis of deaths occurring within the Nottingham trial of faecal occult blood screening for colorectal cancer. *Gut* 2010;59:1088-1093.

Willett CG. Adjuvant therapy for resected rectal cancer. *UpToDate online journal* www.uptodate.com

Winawer SJ, et al. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. *The New England Journal of Medicine* 2000; 342(24):1766-1772.

Winawer SJ, et al. American Cancer Society, Update by the US Multi-Society Task Force on Colorectal Cancer and the Guidelines for Colonoscopy Surveillance after Polypectomy: A Consensus. *Ca-A Cancer Journal for Clinicians* 2006;56:143-159.

Winawer SJ, et al. Colorectal cancer screening. *Best Practice & Research Clinical Gastroenterology* 2007;21(6):1031-1048.

Winawer SJ, et al. Guidelines for colonoscopy surveillance after polypectomy: A consensus update by the US Multi-Society Task Force on colorectal cancer and the American Cancer Society. *Gastroenterology* 2006;130:1872-1885.

Winawer SJ. Screening and surveillance for colorectal cancer: review and rationale. *ACG Annual Postgraduate Course* 2009*:*21- 25.

Wolpin BM, et al. Systematic Treatment of colorectal cancer. *Gastroenterology* 2008;134:1296-1310.

Young J, et al. Serrated pathway colorectal cancer in the population: Genetic consideration. *Gut* 2007;56:1453-1459.

Zbuk Kevin M, et al. Hamartomatous polyposis syndromes. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(9):492-502.

Zhang X., et al. Aspirin use, body mass index, physical activity, plasma C-peptide, and colon cancer risk in US Health professionals. *American Journal of Epidemiology* 2011 Jun 14.

➢ *Miscellaneous*

Archibald L.H., et al. Enhanced recovery after colon surgery in a community hospital system. *Diseases of the Colon and Rectum* 2011;54:840-845.

ASGE Technology Committee, et al. High-resolution and high-magnification endoscopes. *Gastrointestinal Endoscopy* 2009;69:399-407.

Boustany N.N., et al. Microscopic imaging and spectroscopy with scattered light. *Annual Review of Biomedical Engineering* 2010;15:285-314.

Cash BD., et al. Ethnic issues in endoscopy. *Gastrointestinal Endoscopy* 2010;71:1108-1112.

Chande N., et al. Interventions for treating lymphocytic colitis. *Cochrane Database of Systematic Reviews* 2008:CD006096.

Chande N., et al. Interventions for treating lymphocytic colitis. *Cochrane Database of Systematic Reviews* 2008:CD003575.

Kuiper T. and Dekker E. Imaging: NBI-detection and differentiation of colonic lesions. *Nature Review Gastroenterology & Hepatology* 2010;7:128-130.

Marshall J.K., et al. Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. *International journal in gastroenterology* 2010;59:605-611.

Michael J. Stewart, et al. Prednisolone and Budesonide for Short- and Long-Term Treatment of Microscopic Colitis: Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology* 2011;9:881-890.

Swedish K.A., et al. The changing picture of high-grade anal intraepithelial neoplasia in men who have sex with men: the effects of 10 years of experience performing high-resolution anoscopy. *Diseases of the Colon and Rectum* 2011;54:1003-1007.

Tack J., et al. Diagnosis and treatment of chronic constipation – a European perspective. *Neurogastroenterology and Motility* 2011;23:697-710.

Van Rijn, J.C., et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. *The American Journal of Gastroenterology* 2010;101:343-350.

Varadhan K.K., et al. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. *Clinical nutrition* 2010;29:434-440.

➢ *IBS*

Keohane J., et al. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association of reflection of occult inflammation? *The American Journal of Gastroenterology* 2010;105:1788-1794.

Kuicheon Choi,, et al. Impaired Intergrity of DNA After Recovery From Inflammation Causes Persistent Dysfunction of Colonic Smooth Muscle. *Gastroenterology* 2011;141:1293-1301.

Susan A., et al. Mindfulness Training Reduces the Severity of Irritable Bowel Syndrome in Women: Results of a Randomized Controlled Trial. *The American Journal of Gastroenterology* 2011;106:1678-1688.

Whitehead W.E. and Drossman D.A. Validation of symptom-based diagnostic criteria for irritable bowel syndrome: a critical review. *The American Journal of Gastroenterology* 2010;105:814-820.

LIVER

➢ *HAV*

Balart, et al. Viral Hepatitis. *2007 AGA Annual Postgraduate Course*: 198.

Cheney CP. Overview of hepatitis A virus infection in adults. *UpToDate online journal*. www.uptodate.com

Gilroy RK. Hepatitis A. *eMedicine online journal* 2006; www.emedicine.com

Grover PT, et al. Chronic viral hepatitis. *First Principles of Gastroenterology* 2005. pg. 552.

Wikipedia contributors. Hepatitis A. *Wikipedia, the free encyclopedia*. August 14, 2009 at 00:18. Available at http://en.wikipedia.org/wiki/Hepatitis_a.

Wikipedia contributors. Hepatitis A. *Wikipedia, the free encyclopedia*. August 14, 2009 at 00:18. Available at http://en.wikipedia.org/wiki/Hepatitis_a.

➢ *HBV HDV*

Ayoub WS, et al. Review article: current antiviral therapy of chronic hepatitis B. *Alimentary Pharmacology and Therapeutics* 2008;28(2):167-77.

Brunetto MR, et al. Hepatitis B virus surface antigen levels:a guide to sustained response to peginterferon alfa-2a in HbeAg- negative chronic hepatitis B. *Hepatology* 2009;49(4):1141-50.

Buster EH, et al. Peginterferon for chronic hepatitis B. *Best Practice & Research, Clinical Gastroenterology* 2008;22:1093-1108.

Chang TT, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen positive chronic hepatitis B. *Hepatology* 2010;51(2):422-30

Chien RN, et al. Long term nucleos(t)ide analogs therapy for hepatitis B. *Best Practice & Research Clinical Gastroenterology* 2008;22:1081-1092.

De Vries-Sluijs TEMS, et al. Long-term therapy with Tenofovir is effective for patients co-infected with human immunodeficiency virus and Hepatitis B virus. *Gastroenterology* 2010;139:1934-1941.

Degertekin B, et al. Impact of virologic breakthrough and HBIG regimen on hepatitis B recurrence after liver transplantation. *American Journal of Transplantation* 2010;10:1823-1833.

Dienstag JL, et al. American Gastroenterological Association Medical Position Statement on the Management of Hepatitis C. *Gastroenterology* 2006; 130:225–230.

Dusheiko G, et al. Current Treatment of Hepatitis B. *Gut* 2008;57:105-124.

European Association for the Study of the liver. EASL Clinical practice guidelines: Management of chronic hepatitis B. *Journal of Hepatology* 2009;50(2): 227-42.

Heathcote EJ, et al. Three year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011;140:132-143.

Hosel M., et al. Not interferon, but interleukin-6 controls early gene expression in hepatitis B virus infection. *Hepatology* 2009;50:1773-1782.

Hösel, M., et al. Not interferon, but interleukin-6 controls early gene expression in hepatitis B virus infection. *Hepatology.* 2009; 50(6): 1773–1782.

Jacobson IM. Therapeutic options for chronic hepatitis B: considerations and controversies. *The American Journal of Gastroenterology* 2006; 101:S13-S18.

James Fung, et al. Entecavir Monotherapy Is Effective in Suppressing Hepatitis B Virus After Liver Transplantation. *Gastroenterology* 2011;141:1212-1219.

Jimenez-Perez M., et al. Efficacy and safety of entecavir and/or tenofovir for prophylaxis and treatment of hepatitis B recurrence post-liver transplant. *Transplantation Proceedings* 2010;42:3167-3168.

Katz L.H., et al. Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis. *Transplant Infectious Disease* 2010;12:292-308.

Keeffe EB, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clinical Gastroenterology and Hepatology* 2006;4(8):936-62.

Kim B, et al. Validation of FIB-4 and comparison with other simple noninvasive indices for predicting liver fibrosis and cirrhosis in hepatitis B virus infected patients. *Liver International* 2010;30:546-553.

Lacey SR. Hepatitis D. *Emedicine online journal*. www.emedicine.com

Lai CL, et al. Viral Hepatitis B. *The Lancet* 2003; 362(9401):2089-94.

Leemans WF, et al. Success and failure of nucleoside and nucleotide analoguesin chronic hepatitis B. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:171-82.

Liu S., et al. Associations between hepatitis B virus mutations and the risk of hepatocellular carcinoma: a meta-analysis. *Journal of the National Cancer Institute* 2009;101:1066-1082.

Lok A, et al. Chronic Hepatitis B. *Hepatology* 2007;45(2):507-39

Lok AS, et al. Chronic Hepatitis B. *Hepatology* 2007;45(2):507-39. Lok AS, et al. Chronic Hepatitis B: update 2009. *Hepatology* 2009;50(3):661-2

Lok AS, et al. Management of hepatitis B: 2000--summary of a workshop. *Gastroenterology* 2001; 120(7):1828-53.

Lok ASF. Characteristics of the hepatitis B virus and pathogenesis of infection. *UpToDate online journal.* www.uptodate.com

Lok, A. S. F. and McMahon, B. J. Chronic hepatitis B: Update 2009. *Hepatology.* 2009; 50(3): 661–662.

Marcellin P, et al. Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis B. *The New England Journal of Medicine* 2003; 348(9):808-816.

Marcellin P, et al. Sustained response of hepatitis B e antigen negative patients 3 years after treatment with peginterferon alpha 2a. *Gastroenterology* 2009;136(7):2169-2179. e1-4.

Mohanty SR, et al. Treatment of Chronic Hepatitis B. *Nature Clinical Practice Gastroenterology & Hepatology* 2006; 3(8):446-458.

Netanya G., et al. Host Response to Translocated Microbial Products Predicts Outcomes of Patients With HBV or HCV Infection. *Gastroenterology* 2011;141:1220-1230.

Oliviero B., et al. Natural killer cell functional dichotomy in chronic hepatitis B and chronic hepatitis C virus infections. *Gastroenterology* 2099;137:1151-1160.

Papatheodoridis G, et al. The EASL clinical practice guidelines on the management of chronic hepatitis B: the need for liver biopsy. *Journal of Hepatology* 2009;51:226-7

Papatheodoridis G.V., et al. for the HEPNET Greece Cohort Study Group. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *International Journal in Gastroenterology* 2011;60:1109-1116.

Pawlotsky JM, et al. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: Recommendations for a standardized approach. *Gastroenterology* 2008;134:405-415.

Perrillo, et al. Hepatits B and D. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pp. 1647-1672.

Pyrsopoulos NT. Hepatitis B. *eMedicine online journal* 2006; www.emedicine.com

Shamliyan TA, et al. Antiviral therapy for adults with chronic hepatitis B: A systematic Review for the national institute of health consensus development conference. *Annals of Internal Medicine* 2009;150(2):111-124.

Sherlock S, et al. Hepatitis B Virus and Hepatitis Delta Virus. *Diseases of the Liver and Biliary System* (Eleventh Edition) 2002. pg. 285-303.

Sherman M, et al. Management of chronic hepatitis B: consensus guidelines. *The Canadian Journal of Gastroenterology* 2007;21 Suppl C:5C-24C.

Sherman M, et al. The management of chronic viral hepatitis: A Canadian consensus conference 2004. *The Canadian Journal of Gastroenterology* 2004; 18(12);715-28.

Sherman M. Personal view: the management of chronic hepatitis B infection. *Alimentary Pharmacology and Therapeutics* 2006; 23:857-869.

Svicher V., et al. Role of hepatitis B virus genetic barrier in drug-resistance and immune-escape development. *Digestive and Liver Disease* 2011;43:975-983

Terrault N. Benefits and risks of combination therapy for hepatitis B. *Hepatology* 2009;49:S122-8

Teshale E.H., et al. The two faces of hepatitis E virus. *Clinical Infectious Diseases* 2010;51:328-334.

Van Bommel F, et al. Long term efficacy of tenofovir monotherapy for hepatitis B virus monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology* 2010;51:73-80

Van Herck K, et al. Prevention of Viral Hepatitis (B and C) reassessed. *Best Practice & Research Clinical Gastroenterology* 2008;22:6:1009-1029.

Vanlemmens C, et al. Immediate listing for liver transplantation versus standard care for child-Pugh stage B Alcoholic cirrhosis: A Randomized Trial. *Annals of Internal Medicine* 2009;150(3):153-161.

Wasley A., et al. The prevalence of hepatitis B virus infection in the United States era of vaccination. *The Journal of Infectious Diseases* 2010;202:192-201.

Wiseman E, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *The Medical Journal of Australia*. 2009;190(9):489-92.

Woo G, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: A systemic review and Bayesian meta-analyses. *Gastroenterology* 2010;139:1218-1229.

Yang JD, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. *Clinical Gastroenterology and hepatology* 2011;9:64-70

Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. *Hepatology* 2006; 43:S173-S181.

Yuen N.F., et al. Three years of continuous entecavir therapy in treatment-naïve chronic hepatitis B patients: VIRAL suppression, viral resistance, and clinical safety. *American Journal of Gastroenterology* 2011 July;106(7):1264-1271.

➢ **HCV**

Ahlenstiel G, et al. Early Changes in Natural Killer Cell Function Indicate Virologic Response to Interferon Therapy for Hepatitis C. *Gastroenterology* 2011;141:1231-1239.

Ahlenstiel G, et al. Natural killer cells are polarized toward cytotoxicity in chronic hepatitis C in an interferon-alfa-dependent manner. *Gastroenterology* 2010;138:325-335.

Alter G., et al. Reduced frequencies of NKp30+NKp46+, CD161+, and NKG2D+ NK cells in acute HCV infection may predict viral clearance. *Journal of Hepatology* 2010;55:278-288.

Amadei B., et al. Activation of natural killer cells during acute infection with hepatitis C virus. *Gastroenterology* 2010;138:1536-1545.

Arora S., et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *The New England Journal of Medecine* 2011;364:2199-2207.

Aspinall RJ, et al. Review article: the management of side-effects during therapy for hepatitis C. *Alimentary Pharmacology and Therapeutics* 2004; 20:917-929.

Bacon B.R., et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *The New England Journal of Medicine* 2011;364:1207-1217,4.

Balagopal A, et al. *IL28B* and the control of Hepatitis C virus infection. *Gastroenterology* 2010;139:1865-1876

Cheent K. and Khakoo Sl. Natural killer cells and hepatitis C: action and reaction. *International Journal of Gastroenterology and Hepatology* 2011;60:268-278.

Cholongitas E, et al. Novel therapeutic options for chronic hepatitis C. *Alimentary Pharmacology and Therapeutics* 2008;27(10):866-884.

Chopra S. Clinical features and natural history of hepatitis C virus infection. *UpToDate online journal*. www.uptodate.com

Ciesek S. and Manns M.P. Hepatitis in 2010: the dawn of a new era in HCV therapy. *Nature Reviews Gastroenterology and Hepatology* 2011;8:69-71.

Crotta S., et al. Hepatitis C virions subvert natural killer cell activation to generate a cytokine environment permissive for infection. *Journal of Hepatology* 2010;52:183-190.

Davis, Gary L. Treatment of Hepatitis C: Who, how? *2007 AGA Institute Postgraduate Course*:53-70.

Dessouki O., et al. Chronic hepatitis C viral infection reduces NK cell frequency and suppresses cytokine secretion: reversion by anti-viral treatment. *Biochemical and Biophysical Research Communications* 2010;393:331-337.

Di Bisceglie A.M., et al. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. *Hepatology* 2011;53:1100-1108.

Dring M.M., et al. Innate immune genes synergize to predict increased risk of chronic disease in hepatitis C virus infection. *Proceedings of the National Academy of Sciences of the United States* 2011;108:5736-5741.

European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *Journal of Hepatology* 2011;55:245-264.

Everhart J.E., et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. *Gastroenterology* 2009;137:549-557.

Farnik H, et al. Meta-analysis Shows Extended Therapy Improves Response of Patients With Chronic Hepatitis C Virus Genotype 1 Infection. *Clinical Gastroenterology and Hepatology* 2010;8:884-890.

Feld J.J., et al. S-adenosyl methionine improves early viral responses and interferon-stimulated gene induction in hepatitis C nonresponders. *Gastroenterology* 2011;140:830-839.

Ferenci P. Peginterferon and ribavirin in chronic hepatitis C. *Best Practice & Research, Clinical Gastroenterology* 2008;22:1109-1122.

Fernandez-Rodriguez CM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response. *The American Journal of Gastroenterology* 2010;105:2164-2172.

Fontana R.J. and Lok A.S. Noninvasive monitoring of patients with chronic hepatitis C. *Hepatology* 2002;36 (5 suppl 1): S57-64.

Forman LM, et al. The Association between Hepatitis C Infection and Survival after Orthotopic Liver Transplantation. *Gastroenterology* 2002; 122:889–896.

Foster G., et al. Subanalysis of the telaprevir lead-in arm in the REALIZE study: Response at week 4 is not a substitute for prior null response categorization. *Journal of Hepatology* 2011;54(suppl 1):S3-S4.

Freedman ND, et al. Silymarin use and liver disease progression in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis trial. *Alimentary Pharmacology and Therapeutics* 2011;33:127-137.

Gane EJ, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM 1): a randomised, double blind, placebo controlled, dose escalation trial. *The Lancet* 2010;376:1467-1475.

Garcia-Tsao G, et al. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *The American Journal of Gastroenterology.* 2009;104(7):1802-1829.

Ghany M.G., et al. Predicting clinical and histologic outcomes based on standard laboratory tests in advanced chronic hepatitis C. *Gastroenterology* 2010;138:136-146.

Ghany, M. G., et al. Diagnosis, management, and treatment of hepatitis C: An update. *Hepatology.* 2009; 49(4): 1335–1374.

Harrison R.J., et al. Association of NKG2A with treatment treatment for chronic hepatitis C virus infection. *Clinical and Experimental Immunology* 2010;161:306-314.

Hezode C, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *The New England Journal of Medicine* 2009;360:1839-1850.

Hoofnagle JH. A step forward in therapy for hepatitis C. *The New England Journal of Medicine* 2009;360:1899-1901.

Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002; 36(5 Suppl 1):S21-S29.

Jacobson IM, et al. Manifestations of Chronic Hepatitis C Virus Infection Beyond the Liver. *Clinical Gastroenterology and Hepatology* 2010;8:1017-1029.

Jaconson I.M., et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *The New England Journal of Medicine* 2011;364:2405-2416.

Kallwitz E.R., et al. Ethnicity and body mass index are associated with hepatitis C presentation and progession. *Clinical Gastroenterology and Hepatology* 2010;8:72-78.

Kamal SM. Acute Hepatitis C: a systematic review. *The American Journal of Gastroenterology* 2008;103:1283-1297.

Knapp S., et al. A polymorphism in IL28B distinguishes exposed, uninfected individuals from spontaneous resolvers of HCV infection. *Gastroenterology* 2011;141:320-325.

Knapp S., et al. Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. *Hepatology* 2010;51:1168-1175.

Kwo P.Y., et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): An open-label, randomized, multicenter phase 2 trial. *Lancet* 2010 Aug 28;376(9742):705-716.

Lake JR. Immunosuppression and outcomes of patients transplanted for hepatitis C. *Hepatology* 2006; 44:627-629.

Lanford RE, et al. The Accelerating pace of HCV Research: A summary of the 15th International symposium on Hepatitis C virus and related viruses. *Gastroenterology* 2009;136(1):9-16.

Lange C.M., et al. Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. *Journal of Hepatology* 2011;55:322-327.

Lauer GM, et al. Hepatitis C virus infection. *The New England Journal of Medicine* 2001; 345(1):41-52.

Layden T.J., et al. Hepatitis C kinetics: mathematical modeling of viral response to therapy. *Seminars in Liver Disease* 2000;20:173-183.

Lee S., et al. Increased proportion of the CD56(bright) NK cell subset in patients chronically infected with hepatitis C virus (HCV) receiving interferon-alpha and ribavirin therapy. *Journal of Medical Virology* 2010;82:568-574.

Lorenz R. Diagnosis and treatment of acute hepatitis C in adults. *UpToDate online journal.* www.uptodate.com

Manns MP, et al. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006;55:1350-1359.

Marquez R.T., et al. Correlation between microRNA expression levels and clinical parameters associated with chronic hepatitis C viral infection in humans. *Laboratory Investigation* 2010;90:1727-1736.

McHutchison J.G., et al. Telaprevir for previously treated chronic HCV infection. *The New England Journal of Medicine* 2010;362:1292-1303.

McHutchison J.G., et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *The New England Journal of Medicine* 2009;360:1827-1838.

Medrano J, et al. Modeling the probability of sustained virological response to therapy with pegylated interferon plus ribavirin in patients coinfected with hepatitis C virus and HIV. *Clinical Infectious Diseases* 2010;51:1209-1216.

Mengshol JA, et al. Mechanisms of disease: HCV-induced liver injury. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(11):622-634.

Mino O. Rakoski, et al. Mallory-Denk Bodies Are Associated With Outcomes and Histologic Features in Patients With Chronic Hepatitis C. *Clinical Gastroenterology and Hepatology* 2011;9:902-909.

Missiha SB, et al. Disease progression in Chronic Hepatitis C: modifiable and nonmodifiable factors. *Gastroenterology* 2008;134:1699-1714.

Miyagi T., et al. Altered interferon-alpha- signaling in natural killer cells from patients with chronic hepatitis C virus infection. *Journal of Hepatology* 2010;53:424-430.

Mukherjee S. et al. Controversies in liver transplantation for Hepatitis C. *Gastroenterology* 2008;134:1777-1788

Mukherjee S. Hepatitis C. *emedicine online journal*. www.emedicine.com

Oben JA, et al. Fatty liver in chronic hepatitis C infection: unraveling the mechanisms. *Gut* 2007;56(9):1186-1188.

Okoh EJ, et al. HCV in patients with End-stage renal disease. *The American Journal of Gastroenterology* 2008;103(8):2123-2134.

Omland LH, et al. Increased mortality among persons infected with Hepatitis C virus. *Clinical Gastroenterology and Hepatology* 2011;9:71-78.

Parruti G., et al. Rapid prediction of sustained virological response in patients chronically infected with HCV by evaluation of RNA decay 48h after the start of treatment with pegylated interferon and ribavirin. *Antiviral Research* 2010;88:124-127.

Pawlotsky JM, et al. The Hepatitis C virus life cycle as a target for new antiviral therapies. *Gastroenterology* 2007;132:1979-1998.

Pearlman BL. Chronic hepatitis C therapy: changing the rules of duration. *Clinical Gastroenterology and Hepatology* 2006; 4:963-971.

Pelletier S., et al. Increased degranulation of natural killer cells during acute HCV correlates with the magnitude of virus-specific T cell responses. *Journal of Hepatology* 2010;53:805-816.

Podevin P, et al. Production of infectious hepatitis C virus in primary cultures of human adult hepatocytes. *Gastroenterology* 2010;139:1355-1364.

Podevin P, et al. Production of Infectious Hepatitis C Virus in Primary Cultures of Human Adult Hepatocytes. *Gastroenterology* 2010;139:1355-1364.

Poordad F., et al. Boceprevir for untreated chronic HCV genotype 1 infection. *The New England Journal of Medicine* 2011;364:1195-1206.

Sandler, N. G., et al. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. *Gastroenterology*. 2011; 141(4): 1220-1230.

Sarasin-Filipowicz M., et al. Decreased levels of microRNA miR-122 in individuals with hepatitis C responding poorly to interferon therapy. *Nature Medicine* 2009;15:31-33.

Sene D., et al. Hepatitis C virus (HCV) evades NKG2D-dependent NK cell responses through NS5A-mediated imbalance of inflammatory cytokines. *PLoS Pathogens* 2010;6(11).

Sherman K.E., et al. Sustained long-term antiviral maintenance therapy in HCV/HIV-coinfected patients (SLAM-C). *Journal of Acquired Immune Deficiency Syndromes* 2010;55(5):597-605.

Sherman K.E., et al. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naïve genotype 1 HCV patients who achieved and extended rapid viral response: final results of the phase 3 ILLUMINATE study. *Hepatology* 2010;52:401A.

Sherman M, et al. The management of chronic viral hepatitis: A Canadian consensus conference 2004. *The Canadian Journal of Gastroenterology* 2004; 18(12);715-728.

Sherman M. Hepatitis C and Hepatocellular Carcinoma: Grist for the Mill. *Gastroenterology* 2009;136(1): 39-42.

Sherman M. Hepatitis C and Hepatocellular Carcinoma: Grist for the Mill. *Gastroenterology* 2009;136(1): 39-42.

Sklan EH, et al. Mechanisms of HCV survival in the Host. *Nature Review Gastroenterology & Hepatology* 2009;6:217-227.

Stegmann K.A., et al. Interferon-alpha-induced TRAIL on natural killer cells is associated with control of hepatitis C virus infection. *Gastroenterology* 2010;138:1885-1897.

Strader DB, et al. AASLD practice guideline: Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; 39(4) 1147-1171.

Vargas HE. Treatment of hepatitis C 2009: What are the options? *2009 ACG Annual Postgraduate Course*: 157-160.

Weiss JJ, et al. Review article: adherence to medication for chronic hepatitis C—building on the model of human immunodeficiency virus antiretroviral adherence research. *Alimentary Pharmacology and Therapeutics* 2009;30:14-27.

Wong W. Update on chronic hepatitis C. *Clinical Gastroenterology and Hepatology* 2006; 3(6):507-520.

Wursthorn K, et al. Natural History: The importance of viral x, liver damage and HCC. *Best Practice & Research Clinical Gastroenterology* 2008;22:1063-1079.

Yoon Y.H., et al. Alcohol-related and viral hepatitis C-related cirrhosis mortality among Hispanic subgroups in the United States, 2000-2004. *Alcoholism: Clinical and Experimental Research* 2011;35:240-249.

Zeuzem S. Interferon-based therapy for chronic Hepatitis C: current and future perspectives. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(11):610-622.

Zeuzem S., et al. Long-term follow-up of patients with chronic hepatitis C treated with telaprevir in combination with peginterferon alfa-2a and ribavirin: Analysis of the EXTEND study. *Hepatology* 2010;52:401A.

Zeuzem S., et al. Telaprevir for retreatment of HCV infection *The New England Journal of Medicine* 2011;364:2417-2428.

➢ *Fatty Liver Disease*

Adams LA, et al. Nonalcoholic fatty liver disease. *Canadian Medical Association Journal* 2005; 172(7):899-905.

Aithal GP, et al. Randomized, Placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008;135(4):1176-1184.

Angulo P. NAFLD, obesity, and bariatric surgery. *Gastroenterology*, 2006; 130:1848-1852.

Brunt EM, et al. Histopathology of nonalcoholic fatty liver disease. *World Journal of Gastroenterology* 2010;16:5286-5296.

Brunt EM, et al. Nonalcoholic steatohepatitis; a proposal for grading and staging the histological lesions. *American Journal of Gastroenterology* 1999; 94: 2467-2474.

Carter-Kent C, et al. Cytokines in the pathogenesis of Fatty Liver and Disease progression to steatohepatitis: Implications for treatment. *The American Journal of Gastroenterology* 2008;103:1036-1042.

Cassiman D, et al. NASH may be trash. *Gut* 2008;57(2):141-144.

Chalasani N, et al. Relationship of steatosis grade and zonl location to histological feaures of steatohepatitis in adult patients with non-alcoholic fatty liver disease. *Journal of Hepatology* 2008;48:829-834.

Cheung O, et al. Abnormalities of lipid metabolism in nonalcoholic fatty liver disease. *Seminars in Liver Disease* 2008;28:351-359.

Cheung O, et al. Recent advances in nonalcoholic fatty liver disease. *Current Opinion in Gastroenterology* 2009;25:230-237.

Cheung O. and Sanyal A.J. Recent advances in nonalcoholic fatty liver disease. *Current Opinion in Gastroenterology* 2009;25:230-237.

Choi K, et al. Molecular mechanism of insulin resistance in obesity and type 2 diabetes. *Korean Journal of Internal Medicine* 2010;25:119-129.

Chuen-Fei Chen, et al. Changes in Serum Levels of HBV DNA and Alanine Aminotransferase Determine Risk for Hepatocellular Carcinoma. *Gastroenterology* 2011;141:1240-1248.

Comar KM, et al. Review article: drug therapy for non-alcoholic fatty liver disease. *Alimentary Pharmacology and Therapeutics*, 2006;23(2): 207-215.

Cortez-Pinto H, et al. Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH): diagnosis and clinical course. *Best Practice & Research Clinical Gastroenterology* 2004;18(6): 1089-1104.

De Alwis NM, et al. Genetics of Alcoholic Fatty liver disease and non alcoholic fatty liver disease. *Seminars in Liver Disease* 2007;27(1):44-54.

De Ridder RJ, et al. Nonalcoholic fatty liver disease in morbidly obese patients and the effect of bariatric surgery. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:195-201.

Diehl A.M. Hepatic Complications of Obesity. Gastroenterology Clinics of North America 2005;34:45-61.

Farrell GC, et al. Nonalcoholic Fatty Liver Disease: From Steatosis to Cirrhosis. *Hepatology* 2006; 43:S99-S112.

Foster T, et al. Atorvastatin and antioxidants for the treatment of non-alcoholic fatty liver disease: The St Francis Heart Study randomised clinical trial. *The American Journal of Gastroenterology* 2011;106:71-77

Greenfield V, et al. Recent advances in non-alcoholic fatty liver disease. *Current Opinion in Gastroenterology* 2008;24(3):320-7.

Guilherme A, et al. Adipocytes dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews Molecular Cell Biology* 2008;9:367-377.

Harrison SA, et al. Benefits of lifestyle modification in NAFLD.*Gut* 2007:1760-9.

Harte A.l., et al. Elevated endotoxin levels in non-alcoholic fatty liver disease. *The Journal of Inflammation (Lond)* 2010;7:15.

Jarrar MH, et al. Adipokines and cytokines in non-alcoholic fatty liver disease. *Alimentary Pharmacology and Therapeutics* 2008;27(5):412-421.

Jou J, et al. Mechanisms of disease progression in nonalcoholic fatty liver disease. *Seminars in Liver Disease* 2008;28: 370-379.

Kantartzis K, Thamer C, Peter A, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. *Gut* 2009;58:1281-1288.

Kleiner DE, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; 41:1313-1321

Kleiner DE, et al. Nonalcoholic steatohepatitis clinical research network. Design and validation of a histological scoring system for NAFLD. *Hepatology* 2005;41:1313-21.

Lazo M, et al. The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Seminars in Liver Disease.* 2008;28:339-350.

Lefkowitch JH. Steatosis, steatohepatitis and related conditions. In: Lefkowitch JH, ed. Scheuer's Liver Biopsy Interpretation. 8th ed. New York. Saunders-Elsevier. 2010: 93-114.

Loomba R, et al. Placebo in nonalcoholic steatohepatits : insight into natural history and implications for future clinical trials. *Clinical Gastroenterology and Hepatology* 2008;6:1243-1248.

Ludwig J, et al. Nonalcoholic steatohepatitis. Mayo Clinic experiences with a hitherto unnamed disease.   *Mayo Clinic Proceedings* 1980; 55:434-438

Malhi H, et al. Molecular mechanisms of lipotoxity in nonalcoholic fatty liver disease. *Seminars in Liver Disease*. 2008;28:360-369.

Marra F. Nuclear factor-κβ inhibition and non-alcoholic steatohepatitis: inflammation as a target for therapy. *Gut* 2008;57(5):570-572.

McCullough AJ. Thiazolidinediones for Nonalcoholic Steatohepatitis: Promising but Not Ready for Prime Time. *The New England Journal of Medicine* 2006; 355(22):2361-2363.

Mohanty S.R., et al. Influence of ethnicity on histological differences in non-alcoholic fatty liver disease. *Journal of Hepatology* 2009;50:797-804.

Mummadi RR, et al. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*. 2008;6:1396-1402.

Musso G, et al. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology.* 2010; 52: 79-104.

Musso G., et al. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology* 2010;52:79-104.

Nugent C, et al. Evaluation and management of obesity-related non-alcoholic fatty liver disease. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(8):432-41.

Oh MK, et al. Review article: diagnosis and treatment of non-alcoholic fatty liver disease. *Alimentary Pharmacology and Therapeutics* 2008;28(5):503-522.

Preiss D, et al. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. *Clinical Science*. 2008;115:141-150.

Rafiq N, et al. Long- term follow up of patients with nonalcoholic fatty liver. *Clinical Gastroenterology and Hepatology* 2009;7:234-238.

Rakoski MO, et al. Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis. *Alimentary Pharmacology and Therapeutics* 2010; 32:1211-1221.

Ratziu V, et al. Therapeutic trials in nonalcoholic steatohepatitis: insulin sensitizers and related methodological issues. *Hepatology* 2010;52:2206-2215.

Reid, Andrea E. Nonalcoholic fatty liver disease. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006:1793-1802.

Rotman Y., et al. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. *Hepatology* 2010;52:894-903.

Sanyal A.J., et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *The New England Journal of Medicine* 2010;362:1675-1685.

Schwimmer JB, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepathology* 2005; 42: 641-649

Sears D. Fatty Liver. *Emedicine online Journal*. www.author.emedcine.com/topic775.htm

Serino M, et al. Intestinal microflora and metabolic diseases. *Diabetes & Metabolism* 2009;35:262-272.

Shah AG, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clinical Gastroenterology and Hepatology* 2009;7:1104-1112.

Sheth SG. Nonalcoholic steatohepatitis. *UpToDate online journal*. www.uptodate.com

Socha P, et al. Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: A systematic review. *Journal of Pediatric Gastroenterology and Nutrition* 2009; 48:587-596.

Targher G, et al. Risk of cardiovascular disease in patients with non-alcoholic fatty liver disease. *The New England Journal of Medicine* 2010;363:1341-50.

Tendler DA. Pathogenesis of non-alcoholic fatty liver disease. *UpToDate online journal*. www.uptodate.com

Torres DM, et al. Diagnosis and therapy of non-alcoholic steatohepatitis. *Gastroenterology* 2008;134:1682-1698.

Vuppalanchi R, et al. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009;49:306-317.

Wieckowska A, et al. Diagnosis of nonalcoholic fatty liver disease: Invasive versus noninvasive. *Seminars in Liver Disease* 2008;28:386-395.

Wikipedia Contributors. Nonalcoholic fatty liver disease. *Wikipedia, the free encyclopedia*. August 15, 2009. Available at http://en.wikipedia.org/wiki/Nonalcoholic_fatty_ liver_disease.

Williams C.D., et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology* 2011;140:124-131.

Williams CD, et al. Prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis among a largely middle aged population utilizing ultrasound and liver biopsy: A prospective study. *Gastroenterology* 2011;140:124-131.

Younossi ZM. Current management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Alimentary Pharmacology and Therapeutics* 2008;28(1):2-12.

➢ *Alcoholic Liver Disease*

Akriviadis E, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: A double blind placebo controlled trial. *Gastroenterology* 2000;119:1637-1648.

Alexandre Louvet, et al. Early switch to pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids. *Journal of Hepatology* 2008;48:465-470.

Binay Krishna De, et al. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: A randomized controlled trial. *World Journal of Gastroenterology* 2009 April 7; 15(13):1613-1619.

Cohen MS, et al. Review article: the diagnosis and management of alcoholic hepatitis. *Alimentary Pharmacology and Therapeutics* 2009;30:3-13.

De Alwis NM, et al. Genetics of Alcoholic Fatty liver disease and non alcoholic fatty liver disease. *Seminars in Liver Disease* 2007;27(1):44-54.

Field C. and Caetano R. The role of ethnic matching between patient and provider on the effectiveness of brief alcohol interventions with Hispanics. *Alcoholism: Clinical and Experimental Research* 2010;34:262-271.

Field C., et al. Ethnic differences in drinking outcomes following a brief alcohol intervention in the trauma care setting. *Addiction* 2010;105:62-73.

Fiellin DA, et al. Outpatient management of patients with alcohol problems. *Annals of Internal Medicine* 2000; 133:815-827.

Forrest EH, et al. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. *Gut* 2007;56:1743-1746.

Friedman SL. Pathogenesis and frequency of development of alcoholic fatty liver disease. *UpToDate online journal*. www.uptodate.com

Ismail MK. Alcoholic fatty liver. *eMedicine Journal*, Dec 13 2005; 6(12). www.emedicine.com/med/topic99.htm

Lucey MR, et al. Alcoholic hepatitis. *The New England Journal of Medicine* 2009;360:2758-2769.

Mathurin P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *Journal of Hepatology* 2002;36:480-487.

Mihas A. Alcoholic hepatitis. *eMedicine Journal*, Jun 8 2006; 7(6). www.emedicine.com/med/topic101.htm

Nguyen-Khac, E., et al. Glucocorticoids plus N-Acetylcysteine in severe alcoholic hepatitis. *The New England Journal of Medicine.* 2011; 365: 1781-1789.

Niemela O, et al. Biomarkers in Alcoholism. *Clinica Chimica Acta* 2007;377:39-49.

O'Shea RS, et al. Treatment of Alcoholic Hepatitis. *Clinics in Liver Disease* 2005; 9:103-134.

Sauk J. Clinical manifestations and diagnosis of alcoholic liver disease. *UptoDate online journal* 2009. www.uptodate.com

Sauk J. Treatment of alcoholic liver disease. *UptoDate online journal* 2009. www.uptodate.com

Shah V. Alcoholic hepatitis: are we back to prednisone? *ACG Annual Scientific Meeting Symposia Sessions* 2009:64-66.

Tome S, et al. Review article: current management of alcoholic liver disease. *Alimentary Pharmacology and Therapeutics* 2004; 19:707-714.

Tsukamoto H. Conceptual importance of indentifying alcoholic liver disease as a lifestyle disease. *Journal of Gastroenterology* 2007;42(8):603-609.

Wikipedia contributors. Alcoholic Liver disease. *Wikipedia, the free encyclopedia*. August 15, 2009 at 23:27 UTC. Available at http://en.wikipedia.org/wiki/Alcoholic_liver_disease..

Zhang Y., et al. Plasma microRNA-122 as a biomarker for viral-, alocol-, and chemical-related hepatic diseases. *Clinical Chemistry* 2010;56:1830-1838.

> *Autoimmune Hepatitis*

Adams DH, et al. Immunology of the gut and liver: a love/hate relationship. *Gut* 2008;57(6):838-848.

Bjornsson E, et al. Patients with typical laboratory features of autoimmune hepatitis rarely need a liver biopsy for diagnosis. *Clinical gastroenterology and hepatology* 2011;9:57-63

Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. *Clinical Liver Disease* 2002;6:635-647.

Czaja AJ, et al. Advances in the Diagnosis, pathogenesis and management of autoimmune hepatitis. *Gastroenterology* 2010;139:58-72

729

729

729

729

Czaja AJ. Autoimmune hepatitis. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006. pg. 1872-1875.

Heathcote J. Treatment Strategies for Autoimmune Hepatitis. *The American Journal of Gastroenterology* 2006;101:S630–S632.

Hennes EM, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48:169-176Krawitt EL. Autoimmune hepatitis. *The New England Journal of Medicine* 2006;354:54-66.

Krawitt EL. Clinical manifestations and diagnosis of autoimmune hepatitis. *UpToDate online journal*. www.uptodate.com

Krawitt EL. Pathogenesis of autoimmune of hepatitis. *UpTodate online journal*. www.uptodate.com

Krawitt EL. Review article: autoimmune Hepatitis. *The New England Journal of Medicine* 2006; 354:54-66.

Lohse A.W. and Mieli-Vergani G. Autoimmune hepatitis. *Journal of Hepatology* 2011;55:171-182.

Loza, Aldo J Montano, et al. Current therapy for autoimmune hepatitis. *Nature Clinical Practice Gastroenterology & Hepatology* 2007; 4(4):202.

Manns MP, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010;139:1198-1206.

Manns MP, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology.* 2010;51:2193-2213.

Montano-Loza AJ, et al. Risk factors for recurrence of autoimmune hepatitis after liver transplantation. *Liver Transplant* 2009;15:1254-1261.

Montano-Loza AJ, et al. Current therapy for autoimmune hepatitis. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(4):202-214.

Montano-Loza AJ, et al. Features associated with treatment failure in Type 1 Autoimmune Hepatitis and Predictive value of the model of end-stage liver disease. *Hepatology* 2007;46(4):1138-1145.

Silveira MG, et al. Overlap of autoimmune hepatitis and primary biliary cirrhosis: long term outcomes. *The American Journal of Gastroenterology* 2007;102:1244-1250.

Sukerkerk HH. Autoimmune Chronic Active Hepatitis. *Emedicine online journal*. www.emedicine.com

Vivier E., et al. Innate or adaptive immunity? The example of natural killer cells. *Science* 2011;331:44-49.

Wikipedia Contributors. Autoimmune hepatitis. *Wikipedia, the free encyclopedia*. August 8, 2009 at 13:50 UTC. Available at http://en.wikipedia.org/wiki/Autoimmune_hepatitis.

➢ *Primary Biliary Cirrhosis*

Angulo P, et al. Primary biliary cirrhosis. Jaundice. Sleisinger & Fordtran's gastrointestinal and liver disease. *Pathophysiology/Diagnosis/Management* 2006:1885-1896.

Bergasa NV, et al. Primary Biliary Cirrhosis: report of a focus study group. *Hepatology* 2004; 40(4):1013-1020.

Gershwin ME, et al. Risk factors and comorbidities in primary biliary cirrhosis: A controlled interview-based study of 1032 patients. *Hepatology* 2005;42:1194-1202.

Glasova H, et al. Extrahepatic Manifestations of cholestasis. *Journal of Gastroenterology and Hepatology* 2002; 17(9): 938-948.

Heathcote, J. Cholestasis. *First Principles of Gastroenterology* 2005. pg. 590.

Hirschfield GM, et al. Pathogenesis of cholestatic liver disease and therapeutic approaches. *Gastroenterology* 2010;139:1481-1496.

Hirschfield GM, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. *The New England Journal of Medicine* 2009;360:2544-2555.

Hollingsworth KG, et al. Pilot study of peripheral muscle function in primary biliary cirrhosis: potential implications for fatigue pathogenesis. *Clinical Gastroenterology and Hepatology* 2008;6:1041-1048.

John Leung, et al. Colchicine or Methotrexate, With Ursodiol, Are Effective After 20 Years in a Subset of Patients With Primary Biliary Cirrhosis. *Clinical Gastroenterology and Hepatology* 2011;9:776-780.

Jones DE. Pathogenesis of primary biliary cirrhosis. *Gut* 2007;56:1615-1624.

Kaplan MM, et al. Medical Progress: Primary Biliary Cirrhosis. *The New England Journal of Medicine* 2005; 353:1261-1273.

Kaplan MM. Clinical manifestations, diagnosis, and natural history of primary biliary cirrhosis. *UpToDate online journal*. www.uptodate.com

Kaplan MM. Pruritis associated with cholestasis. *UptoDate online journal* 2007. www.uptodate.com

Kremer AE, et al. Pathogenesis and treatment of pruritus in cholestasis. *Drugs* 2008;68(15):2163-2182.

Kuiper EMM, et al. Paris criteria are effective in diagnosis of primary biliary cirrhosis and autoimmune hepatitis overlap syndrome. *Clinical Gastroenterology and Hepatology* 2010;8:530

Kumagi T, et al. Baseline ductopenia and treatment response predict long term histological progression in primary biliary cirrhosis. *The American Journal of Gastroenterology* 2010;105:2186-2194.

Levy C, et al. Pilot study: fenofibrate for patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Alimentary Pharmacology and Therapeutics* 2011;33:235-242.

Liver and intrahepatic bile ducts. www.PathologyOutlines.com

Ludwig J, et al. Staging of chronic nonsupporative destructive cholangitis (syndrome of primary biliary cirrhosis). *Virchows Archiv. A, Pathology Anatomy and Histopathology* 1978;379:103-112.

Mason A, et al.. Primary biliary cirrhosis: new thoughts on pathophysiology and treatment. *Current Gastroenterology Reports* 2002;4:45-51.

Mason AL, et al. Linking human beta retrovirus infection with primary biliary cirrhosis. *Gastroentérologie Clinique et Biologique* 2010;34:359-366.

Metcalf J, et al. The geoepidemiology of primary biliary cirrhosis. *Seminars in Liver Disease* 1997;17:13-22.

Perrillo RP, et al. Hepatitis and cholestasis in a middle-aged woman [clinical conference]. *Hepatology* 1996;24:730-734.

Poupon R. Primary biliary cirrhosis: a 2010 update. *Journal of Hepatology* 2010;52:745-58.

Pyrsopoulos NT. Primary biliary cirrhosis. *eMedicine Journal* 2006;7(5). www.emedicine.com/med/topic223.htm

Reau N. Hepatic ductopenia and vanishing bile duct syndrome. *UpToDate online journal.* www.uptodate.com

Sadamoto T, et al. Expression of pyruvate-dehydrogenase complex PDC-E2 on biliary epithelial cells induced by lymph nodes from primary biliary cirrhosis. *Lancet* 1998;352:1595-1596.

Wasilenko ST, et al. Primary biliary cirrhosis, bacteria and molecular mimicry: what's the molecule and where's the mimic? *Liver International* 2009;29:779-782.

Wikipedia contributors. Primary Biliary Cirrhosis. *Wikipedia, the free encyclopedia.* July 5 2009 at 20:27 UTC. Available at http://en.wikipedia.org/wiki/Primary_biliary_cirrhosis. Accessed August 16 2009.

Xu L, et al. Does a betaretrovirus infection trigger primary biliary cirrhosis? *The Proceedings of the National Academy of Sciences of the United States of America* 2003;100:8454-8459.

Yoshida EM, et al. Autoimmune liver disease and the Canadian First Nations Aboriginal Communities of British Columbia's Pacific Northwest. *World Journal of Gastroenterology* 2006;12:3625-3627.

➢ *Vascular Disorders in the Liver*

Bittencourt PL, et . Portal vein thrombosis and budd-Chiari syndrome. *Clinical Liver Disease* 2009;13(1):127-144.

Caselitz M, et al. Liver Involvement in Osler-Weber-Rendu Disease. In: Boyer TD, Wright TL, Manns MP, eds. Hepatology, A Textbook of Liver Disease. Vol. 2 Fifth edn: Saunders-Elsevier, 2006: 915-929.

DeLeve LD, et al. Vascular disorders of the liver. *Hepatology* 2009;49(5):1729-1764.

DeLeve LD. Sinusoidal Obstruction Syndrome. In: Boyer TD, Wright TL, Manns MP, eds. Hepatology, A textbook of Liver Disease. Vol. 2 Fifth edn: Saunders-Elsevier, 2006: 897-904.

Helmy A. Review article: updates in the pathogenesis and therapy of hepatic sinusoidal obstruction syndrome. *Alimentary Pharmacology & Therapeutics* 2006;23(1):11-25

Herve, et al. Pulmonary vascular abnormalities in cirrhosis. *Best Practice & Research Clinical Gastroenterology* 2007 ; 21(1):141-159.

Kamath, et al. Vascular diseases of the liver. *Mayo Clinic Gastroenterology and Hepatology Board Review, Third Edition* 2008:337-343.

Primignani M. Portal vein thrombosis, revisited. *Digestive and Liver Disease* 2009;42(3):163-170.

Rodruguez-Luna H, et al. Portal and Splenic Vein Thrombosis. In: Boyer TD, Wright TL, Manns MP, eds. Hepatology, A Texbook of Liver Disease. Vol. 2 Fifth edn: Saunders-Elsevier, 2006:905-914.

Sabbà C, et al. Review article: The hepatic manifestations of hereditary haemorrhagic telangiectasia. *Alimentary Pharmacology and Therapeutics* 2008;28(5):523-533.

Spaander VM, et al. Review article: the management of non-cirrhotic non-malignant portal vein thrombosis and concurrent portal hypertension in adults. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:203-209.

Stevens, William E. Vascular diseases of the liver. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006*: pg. 1756.

Tsochatzis EA, et al. Systematic review: portal vein thrombosis in cirrhosis. *Alimentary Pharmacology & Therapeutics* 2010;31(3):366-374.

Valla D. Budd-Chiari Syndrome. Hepatology, A Textbook of Liver Disease. Vol. 2 Fifth edn: Saunders, Elsevier, 2006:877-896.

> *Hemochromatosis and other Hepatic Iron Storage Disorders*

Adams P.C. and Barton J.C. A diagnostic approach to hyperferritinemia with a non-elevated transferring saturation. *Journal to Hepatology* 2011;55:453-458.

Adams PC. Hemochromatosis. *Clinics in Liver Disease* 2004; 8:735-753.

Adams PC. Review article: the modern diagnosis and management of hemochromatosis. *Alimentary Pharmacology and Therapeutics*, 2006: 23:1681-1691.

Adhoute X, et al. Diagnosis of liver fibrosis using FibroScan and other noninvasive methods in patients with hemochromatosis: a prospective study. Gastroenterology Clinical Biology 2008;32:180-187.

Allen KJ, et al. Iron overload related disease in HFE hereditary hemochromatosis. *The New England Journal of Medicine* 2008;358:221-30.

Antonello Pietrangelo. Hereditary Hemochromatosis – A New Look at an Old Disease. *The New England Journal of Medicine* 2004 June 3;350:23.

Antonello Pietrangelo. Hereditary Hemochromatosis: pathogenesis, diagnosis, and the treatment. *Gastroenterology* 2010;139:393-408.

Corradini E, et al. BMP6 Treatment Compensates for the Molecular Defect and Ameliorates Hemochromatosis in Hfe Knockout Mice. Gastroenterology 2010;139:1721-1729.

Crawford DH, et al. Serum hyaluronic acid with serum ferritin accurately predicts cirrhosis and reduces the need for liver biopsy in C282Y hemochromatosis. *Hepatology* 2009;49:418-425.

European Association for the study of the liver. EASL clinical practice guidelines for HFE hemochromatosis. *Journal of Hepatology* 2010;53:3-22.

Ganz T. Hepcidin and iron regulation: ten years later. *Blood* 2011;117:4425-4433.

Gardenghi S., et al. Hepcidin as a therapeutic tool to limit iron overload and improve anemia in eta-thalassemic mice. *The Journal of Clinical Investigation* 2010;120:4466-4477.

Gordeuk VR, Reboussin DM, McLaren CE, et al. Serum ferritin concentrations and body iron stores in a multicenter, multiethnic primary-care population. *American Journal of Hematology* 2008;83(8):618-626.

Griffiths WJ. The genetic basis of hemochromatosis. *Alimentary Pharmacology and Therapeutics* 2007;26(3):331-342.
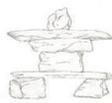
Gurrin LC, et al. The natural history of serum iron indices for HFE C282Y homozygosity associated with hereditary hemochromatosis. *Gastroenterology* 2008;135:1945-52.

Guyatt GH, et al. Going from evidence to recommendations. *British Medical Journal* 2008;336:1049-1051

Guyatt GH, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 2008;336:924-926.

Guyatt GH, et al. Incorporating considerations of resources use into grading recommendations. *British Medical Journal* 2008;336:1170-1173.

Guyatt GH, et al. What is 'quality of evidence' and why is it important to clinicians? *British Medical Journal* 2008;336:995-998

Ioannou GN, et al. Relationship between transferring-iron saturation, alcohol consumption, and the incidence of cirrhosis and liver cancer. *Clinical Gastroenterology and Hepatology* 2007;5:624-629.

Juran BD, et al. Genetics of Hepatobiliary Diseases. *Clinical Gastroenterology and Hepatology*, 2006; 4: 548-557.

Kell D.B. Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. *BMC Medical Genomics* 2009;2:2.

Marro S, et al. Lack of Haptoglobin affects Iron transport across duodenum by modulating ferroportin expression. *Gastroenterology* 2007;133:1261-1271.

Nairz M, et al. Molecular and clinical aspects of iron homeostasis: From anemia to hemochromatosis. *Wiener klinische wochenschrift* 2006;118(15-16):442-462.

Phatak P., et al. A phase I/II, open-label, dose-escalation trial of once daily oral chelator deferasirox to treat iron overload in HFE-realted hereditary hemochromatosis. *Hepatology* 2010;52:1671-1679.

Phatak PD, et al. Hereditary Hemochromatosis: Time for targeted screening. *Annals of Internal Medicine* 2008;149(4):270-272.

Pietrangelo A. Hereditary hemochromatosis – a new look at an old disease. *The New England Journal of Medicine* 2004; 350(23): 2383-2397.

Pietrangelo, et al. Hemochromatosis: An endocrine liver disease. *Heptatology* 2007; 46(4):1291-1300.

Schranz M, et al. Diagnosis of hepatic iron overload: a family study illustrating pitfall in diagnosing hemochromatosis. *Diagnostic Molecular Pathology* 2009;18:53-60.

Schrier SL. Clinical manifestations of hereditary hemochromatosis. *UpToDate online journal*. www.uptodate.com

Schrier SL. Genetics of hereditary hemochromatosis. *UpToDate online journal.* www.uptodate.com

Schrier SL. Pathophysiology and diagnosis of iron over load syndromes. *UpToDate online journal*. www.uptodate.com

Schrier SL. Treatment of Hereditary hemochromatosis. *UpToDate online journal*. www.uptodate.com

Sharma N, et al. The emerging role of the liver in iron metabolism. *The American Journal of Gastroenterology*, 2005; 100:201-206.

Tavill AS, et al. Diagnosis and Management of Hemochromatosis. *Hepatology* 2001; 33(5):1321-1328.

U.S. Preventative Services Task Force. Screening for hemochromatosis: Recommendation statement. *Annals of Internal Medicine*, August 2006. 145(3): 204-208.

Waalen J, Felittin VJ, Gelbart T, et al. Screening for hemochromatosis by measuring ferritin levels: a more effective approach. *Blood* 2008;111:3373-3376.

Wikipedia contributors. Hemochromatosis. *Wikipedia, the free encyclopedia*. August 15, 2006 at 00:06. Available at http://en.wikipedia.org/wiki/ Iron_overload.

➢ *Hepatocellular carcinoma*

Abdalla EK. Overview of treatment approaches for hepatocellular carcinoma. *UpToDate online journal*. www.uptodate.com

Angeli P, et al. Reversal of type 1 hepatorenal syndrome with administration of midodrine and octreotide. *Hepatology* 1999; 29(6):1690-1697.

Bahirwani R, et al. Review article: the evaluation of solitary liver masses. *Alimentary Pharmacology and Therapeutics* 2008;28(8):953-965.

Bhagely Ram Achyut and Li Yang. Transforming Growth Factor-β in the Gastrointestinal and Hepatic Tumor Microenvironment. *Gastroenterology* 2011;141:1167-1178.

Bioulac-Sage P, et al. Hepatocellular Adenoma subtype classification using molecular markers and immunochemistry. *Hepatology* 2007;46:740-748.

Bioulac-Sage P, et al. Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update. *Journal of Hepatology* 2007;45(6):1547-1554.

Bolondi L, et al. Survelliance program of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: A cost effectiveness analysis. *Gut* 2001;48(2): 251-259.

Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *Hepatology* 2003; 39:1076–1084.

Brown RE, et al. Hepatic resection for colorectal liver metastases. *Surgical Clinics of North America* 2010;90(4):839-852.

Brown RS Jr. Asymptomatic Liver Mass. *Gastroenterology* 2006; 131:619–623.

Bruix J, et al. Management of hepatocellular carcinoma. *Hepatology* 2005:42(5):1208-1236.

Bruix J, et al. Management of hepatocellular carcinoma: an update.http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf (version current at July, 2010).

Buell JF, et al. Management of benign hepatic tumours. *Surgical Clinics of North America* 2010;90(4):719-735.

Burak KW, et al. An Evidence-Based Multidisciplinary Approach to the Management of Hepatocellular Carcinoma (HCC): The Alberta HCC Algorithm. *Canadian Journal of Gastroenterology* 2010;24(11):643-650.

Cabibbo G, et al. Multimodal approaches to the treatment of hepatocellular carcinoma. *Nature Clinical Practice Gastroenterology & Hepatology* 2009;6(3):159-69.

Carr BI. Hepatocellular Carcinoma: Current Management and Future Trends. *Gastroenterology* 2004; 127:S218–S224.

Centre for Disease Control and Prevention. Hepatocellular carcinoma – United States, 2001-2006. *Morbidity and Mortality Weekly Report* 2010;59:517-520.

Chopra S. Focal nodular hyperplasia. *UptoDate online journal* 2007. www.uptodate.com

Cucchetti A., et al. Can the dropout risk of candidates with hepatocellular carcinoma predict survival after liver transplantation? *American Journal of Transplantation* 2011;11:1696-1704.

Curry MP. Hepatic adenoma. *UptoDate online journal* 2007. www.uptodate.com

De Jong KP. Review article: multimodality treatment of liver metastases increases suitability for surgical treatment. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:161-9.

Di Bisceglie AM. Issues in Screening and Surveillance for Hepatocellular Carcinoma. *Gastroenterology* 2004; 127:S104–S107.

El-Serag HB, et al. Diagnosis and treatment of Hepatocellular carcinoma. *Gastroenterology* 2008;134:1752-1763.

El-Serag HB, et al. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; 132 (7):2557-2576.

Finegold MJ, et al. Liver tumors: pediatric population. *Liver transplantation* 2008;14(11):1545-1556.

Flavell R.A., et al. The polarization of immune cells in the tumour environment by TGFbeta. *Nature Reviews Immunology* 2010;10:554-567.

Hussain SM, et al. Liver masses. *Magnetic Resonance Imaging Clinics of North America* 2005;13(2):255-275.

Hytiroglou P, et al. Hepatic precancerous lesions and small hepatocellular carcinoma. *Gastroenterology Clinics of North America* 2007;36(4):867-87, vii.

Inman G.J. Switching TGF-beta from a tumor suppressor to a tumor promoter. *Current Opinion in Genetics and Development* 2011;21:93-99.

Ito K, et al. Cirrhosis: MR imaging features. *Magnetic Resonance Imaging Clinics of North America* 2002;10(1):75-92.

Kew, Michael, C. Hepatic tumors and cysts. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 2009.

Llovet JM, et al. Sofenib in advanced hepatocellular carcinoma. *The New England Journal of Medicine* 2008;359:378-390.

Loomba R, et al. Obesity and alcohol synergize to increase the risk of incident hepatocellular carcinoma in men. *Clinical gastroenterology and hepatology* 2010;8:891-898

Lopez PM, et al. Evidence-based management of hepatocellular carcinoma—an update analysis of randomized controlled trials. *Alimentary Pharmacology and Therapeutics* 2006;23(11):1535-1547.

Mamiya T., et al. Reduced transforming growth factor-beta receptor II expression in hepatocellular carcinoma correlates with intragepatic metastasis. *Laboratory Investigation* 2010;90:1339-1345.

Marrero JA, et al. Alpha-fetoprotein, desgamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology* 2009.

Masuzaki, et al. Hepatoclleular carcinoma in viral hepatitis: Improving standard therapy. *Best Practice & Research, Clinical Gastroenterology* 2008;22:1137-1151.

McDonald GB, et al. A problem-oriented approach to liver disease in oncology patients. *Gut* 2008;57:987-1003.

Poultsides GA, et al. Intrahepatic cholangiocarcinoma. *Surgical Clinics of North America* 2010;90(4):817-837.

Reddy SK, et al. Neuroendocrine liver metstases. *Surgical Clinics of North America* 2010;90(4):853-861.

Reid-Lomboardo KM, Skan S, Sclabas, G. Hepatic cysts and liver abscess. *Surgical Clinics of North America* 2010;90(4):679-697.

Schwartz JM. Approach to the patient with a focal liver lesion. *UpToDate Online Journal.* www.uptodate.com

Schwartz JM. Clinical features, diagnosis, and screening for primary hepatocellular carcinoma. *UpToDate online journal*. www.uptodate.com

Schwartz JM. Epidemiology and etiologic associations of hepatocellular carcinoma. *UpToDate online Journal*. www.uptodate.com

Senturk S., et al. Transforming growth factor-beta induces senescence in hepatocellular carcinoma cells and inhibits tumor growth. *Hepatology* 2010;52:966-974.

Sherman, M. Screening for hepatocellular carcinoma. *Best Practice & Research Clinical Gastroenterology* 2005; 19(1):101-118.

Shin S., et al. Foxl1-Cre-marked adult hepatic progenitors have clonogenic and bilineage differentiation potential. *Genes and Development* 2011;25:1185-1192.

Singal A, et al. Meta analysis: Surveillance with ultrasound for early stage hepatocellular carcinoma in patients with cirrhosis. *Alimentary Pharmacology and Therapeutics* 2009.

Spangenberg HC, et al. Targeted therapy for hepatocellular carcinoma. *Nature Reviews Gastroenterology & Hepatology* 2009;6(7):423-432

Stairs D.B., et al. Deletion of p120-catenin results in a tumor microenvironment with inflammation and cancer that establishes it as a tumor suppressor gene. *Cancer Cell* 2011;19:470-483.

Talwalkar JA, et al. Diagnosis and staging of hepatocellular carcinoma. *Gastroenterology* 2004;127(5 Suppl 1):S126-132.

Tranberg K.G. Percutaneous ablation of liver tumours. *Best Practice & Research Clinical Gastroenterology* 2004; 18(1):125-145.

Tsai W.C., et al. MicroRNA-122, a tumor suppressor microRNA that regulates intrahepatic metastasis of hepatocellular carcinoma. *Hepathology* 2009;49:1571-1582.

Washburn K., et al. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. *American Journal of Transplantation* 2010;10:1643-1648.

Welzel T.M., et al. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-medicare database. *Hepatology* 2011;54:463-471.

Wikipedia Contributors. Hepatocellular Carcinoma. *Wikipedia, the free encyclopedia*. August 2, 2009 at 19:01. Available at http://en.wikipedia.org/wiki/Hepatocellular_carcinoma.

Winter SS. Hepatocellular Carcinoma. *Emedicine online journal*. www.emedicine.com

Wong V, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *Journal of Clinical Oncology* 2010 Apr 1;28(10):1660-1665.

Wursthorn K, et al. Natural History: The importance of viral x, liver damage and HCC. *Best Practice & Research, Clinical Gastroenterology* 2008;22:1063-1079.

Yang L., et al. TGF-beta and immune cells: an important regulatory axis in the tumor microenvironment and progression. *Trends in Immunology* 2010;31:220-227.

Zarrinpar A., et al. Liver transplantation for hepatocellular carcinoma: an update. *Hepatobiliary and Pancreatic Diseases International* 2011;10:234-242.

➢ *Congenital Hyperbilirubinemias*

Chowdhury NR. Diagnostic approach to the patient with jaundice or asymptomatic hyperbilirubinemia. *Up to date online Journal* 2007;www.uptodate.com

Chowdhury NR. Gilbert's syndrome and unconjugated hyperbilirubinemia due to bilirubin overproduction. *Up to date online Journal* 2007; www.uptodate.com

Faust TW, et al. Postoperative jaundice. *Clinics in Liver Diseases* 2004;8(1):151-166.

Paré, P. Congenital Hyperbilirubinemias. *First Principles of Gastroenterology* 2005. pg. 528.

Pigazzi A. Crigler-Najjar Syndrome. *Emedicine online journal*. www.emedicine.com

Robertson, M, et al. Approach to the Jaundiced Neonate. *First Principles of Gastroenterology* 2005. pg. 727.

Sabbà C, et al. Review article: The hepatic manifestations of hereditary haemorrhagic telangiectasia. *Alimentary Pharmacology and Therapeutics* 2008;28(5):523-533.

➢ *Drug-Induced Liver Injury*

Agarwal VK, et al. Important elements for the diagnosis of drug-induced liver injury. *Clinical Gastroenterology & Hepatology* 2010;8:463-470.

Athyros VG, et al. Safety and efficacy of long term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A post-hoc analysis. *The Lancet* 2010;376:1916

Chun LJ, et al. Acetaminophen hepatotoxicity and acute liver failure. *Journal of Clinical Gastroenterology* 2009;43(4):342-349.

Daverm T.J., et al. Acute Hepatitis E Infection Accounts for Some Cases of Suspected Drug-Induced Liver Injury. *Gastroenterology* 2011;141:1665-1672.

Fannin RD, et al. Acetaminophen dosing of humans resulting in blood transcriptome and metabolome changes consistent with impaired oxidative phosphorylation. *Hepatology* 2010;51:227-236

Fontana R.J., et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010;52:730-742.

Fontana RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology* 2010;52:730-742.

Fourches D, et al. Cheminformatics analysis of assertions mined from literature that describe drug-induced liver injury in different species. *Chemistry Research and Toxicology* 2010;233;171-183.

Gupta NK , et al. Review article: The use of potentially hepatotoxic drugs in patients with liver disease. *Alimentary Pharmacology and Therapeutics* 2008;28(9):1021.

Hunt CM. Mitochondrial and immunoallergic injury increases risk of positive drug rechallenge after drug-induced liver injury: a systemic review. Hepatology 2010;52:2216-2222.

James LP, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metabolism and Disposition* 2009;37:1779-1784.

Kimura K, et al. Roles of CD44 in chemical-induced liver injury. *Current Opinion in Drug Discovery and Development* 2010;13:96-103.

Kleiner D.E. The patology of drug-induced liver injury. *Seminars in Liver Disease* 2009;29:364-372.

Lee WM. Drug-induced hepatotoxicity. *The New England Journal of Medicine* 2003;349:474-485.

Lewis JH, et al. Efficacy and safety of High-dose pravastatin in Hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled multicentre trial. *Hepatology* 2007;46(5):1453-1463

Liss G., et al. Predicting and preventing acute drug-induced liver injury: what's new in 2010? *Expert Opinion on Drug Metabolism and Toxicology* 2010;6:1047-1061.

Lucena M, et l. Mitochondrial superoxide dismutase and glutathione peroxidase in idiosyncratic drug-induced liver injury. *Hepatology* 2010;52:303-312.

Papay JI, et al. Drug-induced liver injury following positive drug rechallenge. *Regulation Toxicoogy and Pharmacology* 2009;54, 84-90.

Reuben A et al. Drug induced acute liver failure: Results of a U.S multicenter, prospective study. *Hepatology* 2010;52:2065.

Russo M.W., et al. Drug-induced liver injury associated with statins. *Seminars in Liver Disease* 2009;29:412-422.

Senousy BE, et al. Hepatotoxic effects of therapies for tuberculosis. *Nature Review in Gastroenterology and Hepatology* 2010;7:543-556.

Simon JB. Drug-Induced Liver Disease. *First Principles of Gastroenterology* 2005: pg. 583.

Stapelbroek JM, et al. Liver associated with canalicular transport defects: current and futher therapies. Journal of Hepatology 2010;52:258-271.

Teoh Narci C, et al. Liver disease caused by drugs. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: pg. 1842.

Tujios S, Fontana RJ. Mechanisms of drug-induced liver injury: from bedside to bench. *Nature Reviews Gastroenterology and Hepatology* 2011;8:202-211.

Uetrecht J. Immunoallergic drug-induced liver injury in human. *Seminar in Liver Disease* 2009;29:383-392.

Wang K., et al. Circulating microRNAs, potential biomarkers fro drug-induced liver injury. *Proceedings of the National Academy of Sciences of United States* 2009;106:4402-4407.

Watkins PB. Biomarkers for the diagnosis and management of drug induced liver injury. *Seminars in Liver Disease* 2009;29:393-399.

Wijnen PA, et al. Review article: the prevalence and clinical relevance of cytochrome P450 polymorphisms. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:211-219.

> ***Hepatorenal Syndrome***

Angeli, P, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999;29:1690-1697.

Boyer T.D., et al. Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics. *Journal of Hepatology* 2011;55:315-321.

Cardenas A, et al. Therapy Insight: Management of Hepatorenal syndrome. *Nature Clinical Practice Gastroenterology & Hepatology* 2006;3(6):338-348.

Cárdenas, et al. Management of ascites and hepatic hydrothorax. *Best Practice & Research Clinical Gastroenterology* 2007; 21(1): 55-75.

Duvoux, C, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study.

Hepatology 2002;36:374-380.

Gines P, et al. Renal failure in cirrhosis. *The New England Journal of Medicine* 2009;361:1279-1290.

Gluud LL, et al. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010; 51: 576-584.

Guevara M, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology* 1998;28:416-422.

Kuiper JJ, et al. Management of ascites and associated complications in patients with cirrhosis. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:183-193.

McGibbon A, et al. An evidence-based manual for abdominal paracentesis. *Digestive Diseases and Sciences* 2007;52(12):3307-3315.

Moore KP, et al. Guidelines on the management of ascites in cirrhosis. *Gut* 2006; 55:1-12.

Mukherjee S. Hepatorenal Syndrome. *Emedicine online journal.* www.emedicine.com

Ojo AO, et al. Chronic renal failure after transplantation of a nonrenal organ. *The New England Journal of Medicine* 2003;349:931-940.

Pham PT, et al. Review article: current management of renal dysfunction in the cirrhotic patient. *Alimentary Pharmacology and Therapeutics*, 2005; 21:949-961.

Rossle M, et al. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. *Gut* 2010;59:988-1000.

Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009; 49:2087-2107.

Runyon, Bruce A. Ascites and spontaneous bacterial peritonitis. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/ Management* 2006*:* pg. 1946.

Salerno F, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310-1318.

Sanyal AJ, et al. Portal hypertension and its complications. *Gastroenterology* 2008;134:1715-1728.

Wong F, et al. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004;40:55-64.

➢ *Hepatatic Encephalopathy*

Abdalla EK. Overview of treatment approaches for hepatocellular carcinoma. *UpToDate online journal.* www.uptodate.com

Amoros A., et al. Deep sedation with propofol does not precipitate hepatic encephalopathy during elective upper endoscopy. *Gastrointestinal Endoscopy* 2009;70:262-268.

Bajaj JS. Review article: the modern management of hepatic encephalopathy. *Alimentary Pharmacology and Therapeutics* 2010;31(5):537-547.

Bajas JS, et al. Spectrum of neurocognitive impairment in cirrhosis: Implications for the assessment of hepatic encephalopathy. *Hepatology* 2009;50(6):2014-2021.

Bamji N. and Cohen L.B. Endoscopic sedation of patients with chronic liver disease. *Clinics in Liver Disease* 2010;14:185-194.

Bass NM, et al. Rifaximin treatment in hepatic encephalopathy. *The New England Journal of Medicine* 2010; 362(12):1071-81.

Bass NM. The current pharmacological therapies for hepatic encephalopathy. *Alimentary Pharmacology and Therapeutics* 2007;25 Suppl 1:23-31.

Blei AT, et al. Hepatic Encephalopathy. *The American Journal of Gastroenterology* 2001; 96:1968-1976.

Butterworth RF. Pathogenesis of hepatic encephalopathy: new insights from neuroimaging and molecular studies. *Journal of Hepatology* 2003;39(2):278-285.

Córdoba J, et al. Hepatic encephalopathy. *Seminars in Liver Diseases* 2008;28(1):70-80.

Ferenci P, et al. Hepatic encephalopathy-definition, nomenclature, diagnosis and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002; 35(3):716-21.

Ferenci P, Muller CH. Hepatic encephalopathy: treatment. In: Burroughs A, Faegan B, McDonaldJWB (eds). Evidence based gastroenterology. London: *British Medical Journal,* 1999:443.

Fitz, Gregory J. Hepatic Encephalopathy, Hepatopulmonary Syndromes, Hepatorenal syndrome, and Other Complications of Liver Disease. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1979.

Garrow D, et al. Feeding alternatives in patients with Dementia: Examining the evidence. *Clinical Gastroenterology and Hepatology* 2007;5:1372-1378.

Larsen FS, et al. Prevention and management of brain edema in patients with acute liver failure. *Liver Transplantation* 2008;14:S90-96.

Lizardi-Cavera J, et al. Hepatic encephalopathy: a review. *Annals of Hepatology* 2003;2(3):122-130.

Montoliu C., et al. IL-6 and IL-8 in blood may discriminate cirrhotic patients and without minimal hepatic encephalopathy. *Journal of Clinical Gastroenterology* 2009;43:272-279.

Munoz SJ. Hepatic encephalopathy. *Medical Clinics of North America* 2008;92:795-812.

Ortiz M, et al. Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations. *Journal of Hepatology* 2005;42 Suppl(1):S45-53.

Prakash R, et al. Mechanisms, diagnosis and management of hepatic encephalopathy. *Nature Reviews Gastroenterology & Hepatology* 2010;7:515-525.

Riphaus A., et al. Propofol sedation for upper gastrointestinal endoscopy in patients with liver cirrhosis as an alternative to midazolam to avoid acute deterioration of minimal encephalopathy: a randomized, controlled study. *Scandinavian Journal of Gastroenterology* 2009;44:1244-1251.

Romero-Gomez M, et al. Variations in the promoter region of the glutaminase gene and the development of hepatic encephalopathy in patients with cirrhosis. *Annals of Internal Medicine* 2010;153:281-288.

Sass DA, et al. Fulminant Hepatic Failure. *Liver Transplantation* 2005; 11(6):594-605.

Stewart CA, et al. Minimal hepatic encephalopathy. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(12):677-685.

Sundarum V, et al. Hepatic encephalopathy:pathophysiology and emerging therapies. *Medical Clinics of North America* 2009;93(4):819-36.

Takuma Y, et al. Clinical trial: oral zinc in hepatic encephalopathy. *Alimentary Pharmacology and Therapeutics* 2010;32:1080-1090.

Vaquero J, et al. Pathogenesis of hepatic encephalopathy in acute liver failure. *Seminars in Liver Diseases* 2003;23(3):259-269.

Yang X., et al. Portacaval anastomosis-induced hyper-ammonemia does not lead to oxidative stress. *Metabolic Brain Disease* 2010;25:11-15.

➢ *Liver Transplantation*

Aucejo F, et al. Who is at risk for post-transplant lymphoproliferative disorders (PTLD) after liver transplantation? *Hepatology* 2006; 44(1):19-23.

Benten D, et al. Orthotopic liver transplantation and what to do during follow-up: recommendations for the practitioner. *Nature Clinical Practice Gastroenterology & Hepatology* 2009;6(1):23-36.

Brown RS Jr, et al. Managing access to liver transplantation: Implications for Gastroenterology practice. *Gastroenterology* 2007;132:1152-1163.

Cholongitas E., et al. Prioritization for liver transplantation. *Nature Reviews Gastroenterology and Hepatology* 2010;7:659-668.

Clark NM, et al. Infectious complications in liver transplantation. UptoDate online journal 2007; www.uptodate.com

Conti F, et al. Immunosuppressive therapy in liver transplantation. *Hepatology* 2003; 39:664–678.

Cotler SJ, et al. Diagnosis of acute cellular rejection in liver transplantation. UpToDate online Journal. www.uptodate.com

Cotler SJ, et al. Living Donor Liver transplantation. UpToDate online Journal. www.uptodate.com

Dove LM. Et al. Patient selection for liver transplantation. UptoDate online journal 2007; www.uptodate.com

DuBay D., et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. *Annals of Surgery* 2011;253:166-172.

Dufour J-F, et al.What is the current treatment of PTLD after liver transplantation? *Hepatology* 2005; 10:23-26.

Duncan A.W., et al. Stem cells and liver regeneration. *Gastroenterology* 2009;137:466-481.

Eksteen B, et al. Mechanisms of disease: the evolving understanding of liver allograft rejection. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(4):209-219.

Forman LM, et al. The Association between Hepatitis C Infection and Survival after Orthotopic Liver Transplantation. *Gastroenterology* 2002; 122:889–896.

Ginsburg, PM, et al. Diarrhea in Liver Transplant Recipients: Etiology and Management. *Liver Transplantation* 2005;11:881-890.

Helderman JH, et al. Gastrointestinal complications of transplant immunosuppression. *Journal of American Society of Nephrology* 2002;13:277-287.

Keefe EB. Liver Transplantation: Current Status and Novel Approaches to Liver Replacement. *Gastroenterology* 2001;120:749–762.

Kotylar DS, et al. A critical review of candidacy for orthoptopic liver transplantation in Alcoholic liver disease. *American Journal of Gastroenterology* 2008;103:734-743.

Kusne S, et al. Viral and Fungal Infections after Liver Transplantation — PART II. *Liver Transplantation* 2006;12:2–11.

Lake JR. Immunosuppression and outcomes of patients transplanted for hepatitis C. *Hepatology* 2006; 44:627-629.

Lesurtel M. and Clavien P.A. 2010 International consensus conference on liver transplantation for hepatocellular carcinoma. *Liver Transplantation* 2011;17 (suppl 2):S1-5.

Mathur A.K., et al. Racial and ethnic disparities in access to liver transplantation. *Liver Transplantation* 2010;16:1033-1040.

Merion R.M. Current status and future of liver transplantation. *Seminars in Liver Disease* 2010;30:411-421.

Michael R., et al. Frequency and Outcomes of Liver Transplantation for Nonalcoholic Steatohepatitis in the United States. *Gastroenterology* 2011;141:1249-1253.

Mukherjee S, et al. Immediate listing for liver transplantation for alcoholic cirrhosis: Curbing our enthusiasm. *Annals of Internal Medicine* 2009;150(3):216-217.

O'Leary JG, et al. Indications for Liver Transplantation. *Gastroenterology* 2008;134:1789-1801.

Pastor CM, et al.Therapy insight: hepatopulmonary syndrome and orthotopic liver transplantation. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(11):614-621.

Post DJ, et al. Immunosuppression in Liver Transplantation. *Liver Transplantation* 2005;11(11);1307-1314.

Schaubel D., et al. Survival benefit-based deceased-donor liver allocation. *American Journal of Transplantation* 2009;9:970-981.

Schutt VA, et al. Liver diseases unique to pregnancy. *Best Practice in Research & Clinical Gastroenterology* 2007;21(5):771-792.

Sharma P, et al. Management of Pre-Liver Transplantation Patients— Part 1. Liver Transpl 2005; 11(2):124-133.

Vanlemmens C, et al. Immediate listing for liver transplantation versus standard care for child-Pugh stage B Alcoholic cirrhosis: A Randomized Trial. *Annals of Internal Medicine* 2009;150(3):153-161.

Waki K., et al. Outcome of Liver Transplantation for Recipients With Hepatitis B and Hepatitis C Virus Coinfection: Analysis of UNOS Data. *Transplantation* 2011;92:809-814.

Zarrinpar A. and Busuttil R.W. Liver Transplantation: Toward a unified allocation system *Nature Reviews Gastroenterology and Hepatology* 2011;8:542-543.

➢ *Cirrhosis and Portal Hypertension*

Arvaniti V, et al. Infections in patients with cirrhosis increase mortality four fold and should be used in determining prognosis. *Gastroenterology* 2010;139:1246-1256.

Berzigott A., et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology* 2011;54:555-561.

Dienstag J.L., et al. A prospective study of progression in compensated, histologically advanced chronic hepatitis C. *Hepatology* 2011;54:396-405.

Durand F, et al. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *Journal of Hepatology* 2005;42.

Franchis de, et al. Non-invasive diagnosis of cirrhosis and the natural history of it complications. *Best Practice & Research Clinical Gastroenterology* 2007;21(1):3-18.

Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008;134:1655-1669.

Garcia-Tsao G, et al. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C program. *The American Journal of Gastroenterology* 2009;104(7):1802-1829

Greenbaum L.E. and Wells R.G. The role of stem cells in liver repair and fibrosis. *The International Journal of Biochemistry and Cell Biology* 2011;43:222-229.

Jiao J, et al. Hepatic fibrosis. *Current Opinion in Gastroenterology* 2009;25(3):223-229.

Kanwal F, et al. An explicit quality indicator set for measurement of quality of care in patients with cirrhosis. *Clinical Gastroenterology and Hepatology* 2010;8:709

Lewis JH, et al. Efficacy and safety of High-dose pravastatin in Hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled multicentre trial. *Hepatology* 2007;46(5):1453-1463.

Manning DS, et al. Diagnosis and Quantitation of fibrosis. *Gastroenterology* 2008;134:1670-1681.

Martinez Sm, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. *Alimentary Pharmacology and Therapeutics* 2011;33:138-148.

O'Brien A, et al. Nutrition in End-stage liver disease: principles and practice. *Gastroenterology* 2008;134:1729-1740.

Okoh EJ, et al. HCV in patients with End-stage renal disease. *The American Journal of Gastroenterology* 2008;103(8):2123-2134.

Pinzani M, et al. Technology insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. *Nature Clinical Practice Gastroenterology & Hepatology* 2008;5(2):95-106.

Qamar AA, et al. Abnormal haematological indices in cirrhosis. *The Canadian Journal of Gastroenterology* 2009;23(6):441-445.

Robinson KA, et al. Doppler sonography of portal hypertension. *Ultrasound Q* 2009;25(1):3-13.

Teh SH, et al. Risk factors for mortality after surgery in patients with Cirrhosis. *Gastroenterology* 2007;132:1261.

Wolf DC. Cirrhosis. *eMedicine Journal*, Nov 29 2005; 6(11). www.emedicine.com/med/topic3183.htm

Wong F, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut* 2005; 54:718-725.

Yang L., et al. Effectiveness of the PPARgamma agonist, GW570, in liver fibrosis. *Inflammation Research* 2010;59:1061-1071.

Zois CD, et al. Systematic review: Hepatic fibrosis-regression with therapy. *Alimentary Pharmacology and Therapeutics* 2008;28(10):1175-1187.

➢ *Varices PHT*

Bosch J, et al. Prevention of variceal rebleeding. *The Lancet* 2003; 361: 952–954.

Boyer TD, et al. The Role of Transjugular Intrahepatic Portosystemic Shunt in the Management of Portal Hypertension. *Hepatology* 2005; 41(2):386-400.

Boyer TD. Transjugular Intrahepatic Portosystemic Shunt: Current Status. *Gastroenterology* 2003;124:1700-1710.

Burak KW, et al. Portal hypertensive gastropathy and gastric antral vascular ectasia (GAVE) syndrome. *Gut* 2001;49:866-872.

Cardenas A, et al. Therapy Insight: Management of Hepatorenal syndrome. *Nature Clinical Practice Gastroenterology & Hepatology* 2006;3(6):338-348.

Cárdenas, A, et al. Management of ascites and hepatic hydrothorax. *Best Practice & Research Clinical Gastroenterology* 2007;21(1): 55-75.

Dib N, et al. Current management of the complications of portal hypertension: variceal bleeding and ascites. *Canadian Medical Association Journal*, May 9 2006; 174(10):1433-1442.

Duvoux C, et al. Effects of noradrenalin and albumin in patients with type 1 hepatorenal syndrome: a pilot study. *Hepatology* 2002; 36:374-380.

Evans LT, et al. Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. *Hepatology* 2003;37(4): 897-901.

Garcia-Pagan JC, et al. Review article: the modern management of portal hypertension—primary and secondary prophylaxis of variceal bleeding in cirrhotic patients. *Alimentary Pharmacology and Therapeutics* 2008;28(2):178-186.

Garcia-Tsao G, et al. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *The American Journal of Gastroenterology*. 2009;104(7):1802-1829.

Garcia-Tsao G. Portal hypertension. *Current Opinion in Gastroenterology* 2003; 19:250–258.

Garcia-Tsao, et al. Portal hypertension and variceal bleeding- unresolved issues. Summary of an AASLD/EASL single topic conference. *Hepatology* 2008;47(5):1764-1772

Gines P, et al. Management of cirrhosis and ascites. *The New England Journal of Medicine* 2004; 350:1646-1654.

Gines P, et al. Review article: pharmacological treatment of hepatorenal syndrome. *Alimentary Pharmacology and Therapeutics* 2004; 20 (Suppl. 3):57-62.

Gonzalez R, et al. Meta-analysis: combination of endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Annals of Internal Medicine* 2008;149:109-122.

Groszman RJ, et al. Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis. *The New England Journal of Medicine* 2005; 353:2254-2261.

Hay, J. Eileen. Ascites, hepatorenal syndrome, and encephalopathy. *Mayo Clinic Gastroenterology and Hepatology Board Review, Third Edition 2008:*351-361.

Hennenberg M, et al. Mechanisms of extrahepatic vasodilation in portal hypertension. *Gut* 2007;57(9):1300-1314.

Krowka MK. Hepatopulmonary syndromes. *Gut* 2000; 46:1-4.

Kuiper JJ, et al. Management of ascites and associated complications in patients with cirrhosis. *Alimentary Pharmacology and Therapeutics* 2007;26 Suppl 2:183-193.

McGibbon A, et al. An evidence-based manual for abdominal paracentesis. *Digestive Diseases and Sciences* 2007;52(12):3307-15.

Moore KP, et al. Guidelines on the management of ascites in cirrhosis. *Gut* 2006; 55:1-12.

Moore KP, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003; 38(1):258-266.

Mukherjee S. Hepatorenal Syndrome. *Emedicine online journal*. www.emedicine.com

Perini RF, et al. Pathogenesis of portal hypertensive gastropathy: translating basic research into clinical practice. *Nature Clinical Practice Gastroenterology & Hepatology* 2009;6(3):150-158.

Pham PT, et al. Review article: current management of renal dysfunction in the cirrhotic patient. *Alimentary Pharmacology and Therapeutics* 2005;21(8):949-961.

Rimola A, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *Journal of Hepatology* 2000;32(1):142-153.

Robinson KA, et al. Doppler sonography of portal hypertension. *Ultrasound Q* 2009;25(1):3-13.

Rossle M, et al. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. *Gut* 2010;59:988-1000.

Runyon BA, et al. Management of Adult Patients With Ascites Due to Cirrhosis. *Hepatology* 2004; 39(3):841-856.

Runyon BA. Clinical Manifestations of spontaneous bacterial peritonitis. *UptoDate online journal* 2007. www.uptodate.com

Runyon, Bruce A. Ascites and spontaneous bacterial peritonitis. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/ Management* 2006*:* pg. 1946.

Salerno F, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310-1318.

Sanyal AJ, et al. Portal hypertension and its complications. *Gastroenterology* 2008;134:1715-1728.

Sarin SK, et al. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *The New England Journal of Medicine* 1999;340:988-993.

Sarin SK, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. *Gastroenterology* 2010;139:1238-1245

Sharara A, et al. Gastroesophageal variceal hemorrhage. *The New England Journal of Medicine* 2001;345(9):669-681.

Sort P, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *The New England Journal of Medicine* 1999;341:403

Villanueva, et al. Current endoscopic therapy of variceal bleeding. *Best Practice & Research Clinical Gastroenterology* 2008;22(2):261-278.

Wong F, et al. New challenges of hepatorenal syndrome: prevention and treatment. *Hepatology* 2001;34(6):1242-1251.

➢ *Spontaneous Bacterial Peritonitis*

Angeli P, et al. Combined versus sequential diuretic treatment of ascites in nonazotemic patients with cirrhosis: results of an open randomized clinical trial. *Gut* 2010; 59:1-10.

Gines P, et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *Journal of Hepatology* 2010;53:397-417.

Moore KP, et al. The management of ascites – Report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38:258-266.

Runyon B. AASLD Practice Guidelines-Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009;49:2087-2107.

Runyon BA. Clinical Manifestations of spontaneous bacterial peritonitis. *UptoDate online journal* 2007. www.uptodate.com

Senzolo M, et al. Beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver International* 2009;29:1189-1193.

Tandon P, et al. Bacterial infections, sepsis and multi-organ failure. *Seminars in Liver Diseases* 2008; 28: 26-42.

Wong F. The use of TIPS in chronic liver disease. *Annals of Hepatology* 2006; 5: 5-15.

➢ *Miscellaneous*

Everhart J.E. and Ruhl C.E. Burden of digestive diseases in the United States part III: liver, biliary tract, and pancreas. *Gastroenterology* 2009;136:1134-1144.

Furuyama K., et al. Continuous cell supply from Sox9-expressing progenitor zone in adult liver, exocrine pancreas and intestine. *Nature Genetics* 2011;43:34-41.

Ishak K., et al. Histological grading and staging of chronic hepatitis. *Journal of Hepatology* 1995;22:696-699.

Jiang N., et al. Targeted gene silencing of TLR4 using liposomal nanoparticles for preventing liver ischemia reperfusion injury. *American Journal of Transplantation* 2011 Sep 11;9:1835-1844.

Laterza O.F., et al. Plasma microRNAs as sensitive and specific biomarkers of tissue injury. *Clinical Chemistry* 2009;55:1977-1983.

Omary M.B., et al. Toward unraveling the complexity of simple epithelial keratins in human disease. *Journal of Clinical Investigation* 2009;119:1794-1805.

Puoti C., et al. HCV carriers with normal alanine aminotransferase levels: healthy persons or seversly ill patients? Dealing with an everday clinical problem. *European Journal of Internal Medicine* 2010;21:57-61.

Torre C., et al. Molecular determinants of liver zonation. *Progress in Molecular Biology and Translational Science* 2010;97:127-150.

Yanger K. and Stanger B.Z. Facultative stem cells in liver and pancreas: fact and fancy. *Developmental Dynamics* 2011;240:521-529.

Yves Deugnier, et al. Improvement in Liver Pathology of Patients With β-Thalassemia Treated With Deferasirox for at Least 3 Years. *Gastroenterology* 2011;141:1202-1211.

BILIARY TREE

Binenbaum SJ, et al. Single-incision laparoscopic cholecystectomy using a flexible endoscope. Archives of Surgery 2009;144(8):734-738.

Bowlus CL, et al. Primary sclerosing cholangitis in genetically diverse populations listed for liver transplantation: unique clinical and human leukocyte antigen associations. *Liver Transplantation.* 2010;16(11):1324-30.

Carpentier R, et al. Embryonic ductal plate cells give rise to cholangiocytes, periportal hepatocytes, and adult liver progenitor cells. *Gastroenterology.* 2011;141(4):1432-8, 1438.e1-4.

Center SA, et al. Diseases of the Gallbladder and Biliary Tree. *Veterinary Clinics of North America: Small Animal Practice* 2009;39(3):543-598.

Chaput U, et al. Temporary placement of partially covered self-expandable metal stents for anastomotic biliary strictures after liver transplantation: a prospective, multicenter study. *Gastrointestinal Endoscopy.* 2010;72(6):1167-74.

Costamagna G, et al. Endotherapy of postoperative biliary strictures with multiple stents: results after more than 10 years of follow-up. *Gastrointestinal Endoscopy.* 2010;72(3):551-7.

Dauer M, et al. Mandatory and optional function test for biliary disorders. *Best Practice in Research Clinical Gastroenterology* 2009;23(3):441-451.

Gilani SN, et al. Collin's sign:validation of a clinical sign in cholelithiasis. *Irish Journal of Medical Sciences* 2009; 178(4):397-400.

Halldestam I, et al. Incident of and potential risk factors for gallstone disease in a general population sample. *British Journal of Surgery* 2009;96(11);1315-1322.

Hu B, et al. Endoscopic stenting for post-transplant biliary stricture: usefulness of a novel removable covered metal stent. *Journal of Hepato-Biliary-Pancreatic Sciences.* 2011;18(5):640-5.

Johnson L. Factors That Predict Relief From Upper Abdominal Pain After Cholecystectomy. *Clinical Gastroenterology and Hepatology* 2011;9:891-896.

Lawrence C, et al. Low symptomatic premature stent occlusion of multiple plastic stents for benign biliary strictures: comparing standard and prolonged stent change intervals. Gastrointestinal Endoscopy. 2010;72(3):558-63.

Lemaigre FP. Molecular mechanisms of biliary development. *Progress in Molecular Biology and Translational Science.* 2010;97:103-126.

Li VKM, et al. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. *Surgical Endoscopy* 2009; 23:1640-1644.

Mahid SS, et al. Meta-analysis of cholecystectomy in symptomatic patients with positive hepatobiliary iminodiacetic acid scan results without gallstones. Archives of Surgery 2009:144(2):180-187.

NIH state-of-the science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. NIH Consensus State of Sciences Statements 2002:19(1):1-26.

Park do H, et al. Anchoring flap versus flared end, fully covered self-expandable metal stents to prevent migration in patients with benign biliary strictures: a multicenter, prospective, comparative pilot study (with videos). *Gastrointestinal Endoscopy.* 2011;73(1):64-70.

Portincasa P, et al. Cholesterol gallstone disease. *Lancet* 2006: 368(9531):230-239.

Shaffer EA, et al. Epideniology and risk factors for gallstone disease: has the paradigm changed in the 21st century?. *Current Gastroenterology Report* 2005;7(2):132-140.

Shanbhogue AK, et al. Benign biliary strictures: a current comprehensive clinical and imaging review. *American Journal of Roentgenology.* 2011;197(2):W295-306.

Van Boeckel, et al. Plastic or metal stents for benign extrahepatic biliary strictures: a systematic review. BCM Gastroenterology 9,96 (2009).

Wang HH, et al. New insights into the molecular mechanisms underlying effects of estrogen on cholesterol gallstone formation. *Biochimica et Biophysica Acta* 2009; 1791(11):1037-1047.

Yao CC, et al. Assessment of common bile duct using laparoscopic ultrasound during laparoscopic cholecystectomy. *Surgery Laparoscopy Endoscopy & Percutaneous Techniques* 2009; 19(4):317-320.

Zaliekas J, et al. Complications of gallstones: the Mirizzi syndrome, gallstone ileus, gallstone pancreatitis, complications of "lost gallstones. *Surgical Clinic of North America* 2008; 88(6):1345-1368.

Zepada-Gomez S. and Baron T.H. Benign biliary strictures: current endoscopic management. *Nature Reviews Gastroenterology and Hepatology* 2011;8:573-581.

GALLBLADDER

Banim PJR, et al. The aetiology of symptomatic gallstones quantification of the effects of obesity, alcohol and serum lipis on risk. Epidemiological and biomarker data from a UK prospective cohort study (EPIC-Norfolk). *European Journal of Gastroenterology & Hepatology.*2011;23:733-740.

Gurusamy K, et al. Systematic review and meta-analysis of intraoperative versus preoperative endoscopic sphincterotomy in patients with gallbladder and suspected common bile duct stones. *British Journal of Surgery.*2011;98:908-916.

Ito H, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Annals of Surgery.* 2011 Aug;254(2):320-5.

Kirk G, et al. Preoperative symptoms of irritable bowel syndrome predict poor outcome after laparoscopic cholecystectomy. *Surgical Endoscopy.* 2011;25(10):3379-84.

Ma J, et al. Randomized controlled trial comparing single-port laparoscopic cholecystectomy and four-port laparoscopic cholecystectomy. *Annals of Surgery.* 2011;254(1):22-7.

Mertens MC, et al. Risk assessment in cholelithiasis: is cholecystectomy always to be preferred? *Journal of Gastrointestinal Surgery.* 2010;14(8):1271-9.

Pfluke JM and Bowers SP Jr. Laparoscopic intraoperative biliary ultrasonography: findings during laparoscopic cholecystectomy for acute disease. *Journal of Laparoendoscopic & Advanced Surgical Techniques.* 2011;21(6):505-9.

Schmidt M, et al. A 24-year controlled follow-up of patients with silent gallstones showed no long-term risk of symptoms or adverse events leading to cholecystectomy. *Scandinavian Journal of Gastroenterology.* 2011;46(7-8):949-54.

Thistle JL, et al. Factors that predict relief from upper abdominal pain after cholecystectomy. *Clinical Gastroenterology and Hepatology.* 2011;9(10):891-6.

PANCREAS

➤ *Pancreatitis*

Acute Pancreatitis Classification working Group. Revision of the Atlanta classification of acute pancreatitis. Available at: http://www.pancraasclub.com/resources/Atlantaclassification.pdf.

Bollen TL, et al. Comparative evaluation of the modified CT severity index and CT severity index in assessing severity of acute pancreatitis. *American Journal of Roentgenology.* 2011;197(2):386-92.

Cornett D.D., et al. The causes and outcome of acute pancreatitis associated with serum lipase > 10,00 U/L. *Digestive Diseases and Sciences* 2011 May 26.

Cornett DD, et al. The causes and outcome of acute pancreatitis associated with serum lipase >10, et al.000 u/l. *Digestive Diseases and Sciences.* 2011;56(11):3376-81.

Fieker A, et al. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clinical and Experimental Gastroenterology.*2011; 4: 55–73.

Gardner TB, et al.Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. *Gastrointestinal Endoscopy.* 2011;73(4):718-26.

Gregersen N and Bross P. Protein misfolding and cellular stress: an overview. *Methods in Molecular Biology.* 2010;648:3-23.

Hjalmar C. van Santvoort, et al. A Conservative and Minimally Invasive Approach to Necrotizing Pancreatitis Improves Outcome. *Gastroenterology* 2011; 141:1254-1263.

Horvath K, et al. Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. *Archives of Surgery.* 2010 Sep;145(9):817-25.

Kim HS, et al. The role of intraductal US in the management of idiopathic recurrent pancreatitis without a definite cause on ERCP. *Gastrointestinal Endoscopy.* 2011;73(6):1148-54.

Lugea A, et al. Adaptive unfolded protein response attenuates alcohol-induced pancreatic damage. *Gastroenterology.* 2011 Mar;140(3):987-97.

Matsumoto I, et al. A focal mass-forming autoimmune pancreatitis mimicking pancreatic cancer with obstruction of the main pancreatic duct. *Journal of Gastrointestinal Surgery.* 2011;15(12):2296-8.

Paul MD and Mooney DP. The management of pancreatic injuries in children: operate or observe. *Journal of Pediatric Surgery.* 2011;46(6):1140-3.

Petrov MS, et al. Organ Failure and Infection of Pancreatic Necrosis as Determinants of Mortality in Patients With Acute Pancreatitis. *Gastroenterology* 2010;139: 813-820.

van Santvoort HC, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology.* 2011;141(4):1254-63.

van Santvoort HC, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *The New England Journal of Medicine.* 2010 Apr 22;362(16):1491-502.

Williams JA. Regulation of acinar cell function in the pancreas. *Current Opinion in Gastroenterology.* 2010;26(5):478-83.

➢ *Neoplasia*

Benjamin M. Weinberg, et al. Asymptomatic Pancreatic Cystic Neoplasms: Maximizing Survival and Quality of Life Using Markov-Based Clinical Nomograms. ***Gastroenterology* 2010;**138:531-540.

Crane CH, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. *Journal of Clinical Oncology.* 2011;29(22):3037-43.

Davì MV, et al. Presentation and outcome of pancreaticoduodenal endocrine tumors in multiple endocrine neoplasia type 1 syndrome. *Neuroendocrinology.* 2011;94(1):58-65.

DeWitt J, et al. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. *Gastrointestinal Endoscopy.* 2010;72(4):862-6.

Fottner, C., et al. *In Vivo* Molecular Imaging of Somatostatin Receptors in Pancreatic Islet Cells and Neuroendocrine Tumors by Miniaturized Confocal Laser-Scanning Fluorescence Microscopy. *Endocrinology.* 2010;151(5):2179–2188.

Furuyama K, et al. Continuous cell supply from a Sox9-expressing progenitor zone in adult liver, exocrine pancreas and intestine. *Nature Genetics.* 2011;43(1):34-41.

Hartwig W, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. *Annals of Surgery.* 2011;254(2):311-9.

Kang MJ, et al. Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. *Clinical Gastroenterology and Hepatology.* 2011;9(1):87-93.

Kudo Y, et al. Incidence of and risk factors for developing pancreatic cancer in patients with chronic pancreatitis. *Hepatogastroenterology.* 2011;58(106):609-11.

Lin JL, et al. Negative predictive value of positron emission tomography/computed tomography in patients with a clinical suspicion of pancreatic cancer. *Pancreas.* 2011;40(5):653-6.

Morris JP 4th, et al. Beta-catenin blocks Kras-dependent reprogramming of acini into pancreatic cancer precursor lesions in mice. *Journal of Clinical Investigation.* 2010;120(2):508-20.

Nau P, et al. Diagnostic transgastric endoscopic peritoneoscopy: extension of the initial human trial for staging of pancreatic head masses. *Surgical Endoscopy.* 2010;24(6): 1440-1446.

Pausawasdi N, et al. Long-term follow-up of patients with incidentally discovered pancreatic cystic neoplasms evaluated by endoscopic ultrasound. *Surgery.* 2010;147(1):13-20.

Raraty MG, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Annals of Surgery.* 2010;251(5):787-93.

Sadakari Y, et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. *Pancreas.* 2010;39(2):232-6.

Sahani DV, et al. Prospective evaluation of reader performance on MDCT in characterization of cystic pancreatic lesions and prediction of cyst biologic aggressiveness. *American Journal of Roentgenology.* 2011;197(1):W53-61.

Schlingensiepen KH, et al. Transforming growth factor-beta 2 gene silencing with trabedersen (AP 12009) in pancreatic cancer. *Cancer Science.* 2011;102(6):1193-200.

van Geenen EJ, et al. Smoking is related to pancreatic fibrosis in humans. *The American Journal of Gastroenterology.* 2011;106(6):1161-6; quiz 1167.

Weinberg BM, et al. Asymptomatic pancreatic cystic neoplasms: maximizing survival and quality of life using Markov-based clinical nomograms. *Gastroenterology.* 2010;138(2):531-40.

➤ *ERCP*

Atsushi Sofuni, et al. Endoscopic Pancreatic Duct Stents Reduce the Incidence of Post–Endoscopic Retrograde Cholangiopancreatography Pancreatitis in High-Risk Patients. *Clinical Gastroenterology and Hepatology* 2011;9: 851-855.

Chahal P, et al. Short 5Fr vs long 3Fr pancreatic stents in patients at risk for post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clinical Gastroenterology and Hepatology.* 2009;7(8):834-9.

Chan HH, et al. Endoscopic papillary large balloon dilation alone without sphincterotomy for the treatment of large common bile duct stones. *BMC Gastroenterology.* 2011; 11: 69.

Cote G.A., et al. Difficult biliary cannulation: use of physician-controlled wire-guided cannulation over a pancreatic duct stent to reduce the rate of precut sphincterotomy (with video). *Gastrointestinal Endoscopy.* 2010;71(2):275-9.

Dumonceau JM, et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy.* 2010;42(6):503-15.

Gardner TB and Gordon SR. Interobserver agreement for pancreatic endoscopic ultrasonography determined by same day back-to-back examinations. *Journal of Clinical Gastroenterology.* 2011;45(6):542-5.

Kalva SP, et al. Angiographic intervention in patients with a suspected visceral artery pseudoaneurysm complicating pancreatitis and pancreatic surgery. *Archives of Surgery.* 2011;146(6):647-52.

Kennedy PT, et al. The safety and utility of prophylactic pancreatic duct stents in the prevention of post-ERCP pancreatitis: an analysis of practice in a single UK tertiary referral center. *Surgical Endoscopy.* 2010;24(8):1923-8.

Kevin E Woods and Field F Willingham. Endoscopic retrograde cholangiopancreatography associated pancreatitis: A 15-year review. *World Journal of Gastrointestinal Endoscopy.* 2010; 2(5): 165-178.

Mazaki T, et al. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis. *Endoscopy*. 2010;42(10):842-53.

Muralidharan V and Jamidar P. Pharmacologic prevention of post-ERCP pancreatitis: is nitroglycerin a sangreal? *Gastrointestinal Endoscopy.* 2006 ;64(3):358-60.

Sofuni A, et al. Endoscopic pancreatic duct stents reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients. *Clinical Gastroenterology and Hepatology.* 2011;9(10):851-8; quiz e110.

Testoni PA, et al. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. *The American Journal of Gastroenterology.* 2010;105(8):1753-61.

Yoo KS, et al. Nafamostat mesilate for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a prospective, randomized, double-blind, controlled trial. *Pancreas.* 2011;40(2):181-6.

Zolotarevsky E, et al. Prophylactic 5-Fr pancreatic duct stents are superior to 3-Fr stents: a randomized controlled trial. *Endoscopy.* 2011;43(4):325-30.

➢ *Miscellaneous*

Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis. *British Journal of Surgery.* 2011;98(10):1446-54.

Gonoi W, et al. Pancreas divisum as a predisposing factor for chronic and recurrent idiopathic pancreatitis: initial in vivo survey. *Gut.* 2011;60(8):1103-8.

Heetun ZS, et al. Biliary sphincter of Oddi dysfunction: response rates after ERCP and sphincterotomy in a 5-year ERCP series and proposal for new practical guidelines. *European Journal of Gastroenterology & Hepatology.* 2011;23(4):327-33.

NUTRITION IN GASTROINTESTINAL DISEASE

Baker JP, et al. Nutritional assessment: a comparison of clinical judgement and objective measurements. *The New England Journal of Medicine* 1982;306:969-972

Blackburn GL, et al. Nutritional and metabolic assessment of the hospitalized patient. *Journal of Parenteral and Enteral Nutrition* 1977;1:11-22.

Goldwasser P, et al. Association of serum albumin and mortality risk. *Jouranl of Clinical Epidemiology* 1997; 50:693-703.

Jeejeebhoy KN. Nutritional assessment. *Gastroenterology Clinics of North America* 1998;27(2): 347-369.

Klein S, et al. AGA technical review on obesity. *Gastroenterology* 2002; 123:882-932.

Rombeau JL, Rolandelli RH (eds.). Clinical nutrition: enteral and tube feeding. 3rd ed. Philadelphia: WB Saunders, 1997.

Rombeau JL, Rolandelli RH (eds.). Clinical nutrition: parenteral nutrition. 3rd ed. Philadelphia: WB Saunders, 2001.

Waitzberg DL, et al. Nutritional assessment in the hospitalized patient. *Current Opinion in Clinical Nutrition & Metabolic Care* 2003;6(5):531-538.

Yang C.S. and Wang H. Mechanistic issues concerning cancer prevention by tea catechins. *Molecular Nutrition and Food Research* 2011;55:819-831.

MISCELLANEOUS

Albert Dahan, et al. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology* 2010; 112:226 –38.

Altekruse SF, et al. SEER Cancer Statistics Review 1975-2007, National Cancer Institute. Bethesda, MD,. based on November 2009 SEER data submission, posted to the SEER Web site, 2010. Available at: http://seer.cancer.gov/csr/1975_2007/. Accessed: April 15, 2011.

CDC/NCHS National health Interview Survey, 1997-2009, Sample Adult Core component. Available at: http://www.cdc.gov/nchs/data/nhis/earlyrelease/2010 06_09.pdf. Accessed December 8, 2010.

Centers for Disease Control and Prevention. National Center for health Statistics. Health Data Interactive. Available at: http://www.cdc.gov/nchs/hdi.htm. Accessed August 10, 2010.

Clinical evidence BMJ group. *British Medical Journal.* 2010. Available at: http://clinicalevidence.bmj.com.

Heneghan S, et al. Society of American Gastrointestinal Endoscopic Surgeons (SAGES) guidelines for office endoscopic services. Surgical Endoscopy. 2009 May;23(5):1125-9.

Jemal A., et al. Global cancer statistics. *Ca-A Cancer Journal for Clinicians.* 2011;61:69-90.

Kellow JE. Introduction: a practical evidence-based approach to the diagnosis of the functional gastrointestinal disorders. *The American Journal of Gastroenterology.* 2010;105(4):743-6.

Khashab MA and Kalloo AN. Critical analysis of hot topics in NOTES. *Nature Review Gastroenterology & Hepatology.* 2011 Sep 6;8(10):565-72. doi: 0.1038/nrgastro.2011.150.

Kwak MK and Kensler TW. Targeting NRF2 signaling for cancer chemoprevention. *Toxicology and Applied Pharmacology.* 2010;244(1):66-76.

Lee CK, et al. Balanced propofol sedation for therapeutic GI endoscopic procedures: a prospective, randomized study. *Gastrointestinal Endoscopy.* 2011;73(2):206-14.

Peterson J and Pasricha PJ. Regenerative medicine and the gut. *Gastroenterology.* 2011;141(4):1162-6, 1166.e1-2.

Porter ME. What is value in health care? *The New England Journal of Medicine.* 2010;363:2477-2481.

Rex DK, et al. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology.* 2009;137(4):1229-37; quiz 1518-9.

Rich EC, et al. The implications of comparation effectiveness research for academic medicine. *Academic Medicine.* 2011;86:684-688.

Santos BF and Hungness ES. Natural orifice translumenal endoscopic surgery: progress in humans since white paper. *World Journal of Gastroenterology.* 2011;17(13):1655-65.

Savin,T, et al. On the growth and form of the gut. *Nature* 2011;476:57-62

US Census Bureau. US and world population clocks. Available at: http://www.census.gov/main/www/popclock.html. Accessed October 7, 2010.

Vargo J. J., et al. Position statement: nonanesthesiologist administration of propofol for GI endoscopy. *Gastrointestinal Endoscopy*. 2009;70:1053-1059.

Vargo, J.J. Procedural sedation. *Current Opinion in Gastroenterology.* 2010;26:421-424.

List of Contributors

ADAMS, P.C., London Health Sciences Centre-University Campus,
339 Windermere Rd., London, ON N6A 5A5.
Tel: (519) 858-5125 Fax: (519) 858-5114 E-mail: padams@uwo.ca

ALLARD, J.P., University Health Network-Toronto General Hospital,
EW 217A-200 Elizabeth St., Toronto, ON M5G 2C4.
Tel: (416) 340-5159 Fax: (416) 348-0065 E-mail: johane.allard@utoronto.ca

ASPINALL, A. I., Department of Medicine, Teaching Research Wellness Building,
1403 - 29 Street NW, Calgary, AB T2N 2T9.
Tel: (403) 592-5049 Fax: (403) 592-5090 Email: aaspinal@ucalgary.ca

BAIN, V.G., University of Alberta, 205 College Plaza, 8215- 112th St.,
Edmonton, AB T6G 2C8.
Tel: (780) 492-8128 Fax: (780) 492-8130 E-mail: vince.bain@ualberta.ca

BURAK, K., Department of Medicine, Teaching Research Wellness Building,
University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 2T9.
Tel: (403) 592-5049 Fax: (403) 592-5090 E-mail: kwburak@ucalgary.ca

BURNSTEIN, M., Interim Division, General Surgery, University of Toronto,
St. Michael's Hospital, 38 Shuter St., Suite 504, Toronto, ON M5B 1A6.
Tel: (416) 864-6050 Fax: (416) 864-5668 E-mail: burnsteinm@smh.toronto.on.ca

BURSEY, R.F., Associate Professor of Medicine, Memorial University,
Health Sciences Centre, 300 Prince Philip Dr., St. John's, NL A1B 3V6.
Tel: (709) 777-6960 Fax: (709) 777-8044 E-mail: fbursey@mun.ca

CARPENTIER, S., Division of Gastroenterology, Department of Medicine, McGill University, Royal Victoria
Hospital, 687 Pine Ave West, R.2.28, Montreal, QC H3A1A1
Tel: (514)843-1616; Fax: (514)843-1421 E-mail: scarpentier@dal.ca

CHAMPION, M.C., Internal Medicine/Gastroenterology, The Ottawa
Hospital-Civic Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4674 Fax: (613) 761-5269 E-mail: mchampion@ottawahospital.on.ca

CLANDININ, M. T., Department of Agricultural, Food & Nutritional Science,
University of Alberta, 4-002C Li Ka Shing Ctr for Hlth Rsch Innovation, Edmonton,
AB T6G 2E1
Tel: 780.492.5188 **Fax:** 780.492.8855 **E-mail:** tclandinin@professorpufa.com

COFFIN, C.S., Department of Medicine, Teaching Research Wellness Building,
University of Calgary, 3280 Hospital DR NW, Calgary T2N4Z6.
Tel: (403) 592-5049 Fax: (403) 592-5038 E-mail: cscoffin@ucalgary.ca

CONGLY, S. E., Department of Medicine, Teaching Research Wellness Building,
1403 - 29 Street NW, Calgary, AB T2N 2T9.
Tel: (403) 592-5049 Fax: (403) 592-5090 E-mail: stephencongly@gmail.com

DUBÉ, C., Division of Gastroenterology, The Ottawa Hospital,
1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4603 Fax: (613) 761-5068 E-mail: cdube@ottawahospital.on.ca

FARDY, J.M., Gastroenterology/Internal Medicine, Memorial University,
Faculty of Medicine, Health Sciences Centre, 300 Prince Philip Dr.,
St John's, NF A1B 3V6.
Tel: (709) 777-7064 Fax: (709) 777-8044 E-mail: jfardy@morgan.ucs.mun.ca

FREEMAN, H.J., Gastroenterology, UBC Hospital, 2211 Wesbrook Mall,
Vancouver, BC V6T 1W5. E-mail: hugfree@shaw.ca

GAISANO, H., University Health Network, Toronto Western Hospital,
6B Fell 6-176, 399 Bathurst St., Toronto, ON M5T 2S8.
Tel: (416) 603-5949 E-mail: herbert.gaisano@utoronto.ca

GRÉGOIRE, S., Gastroenterology, The Ottawa Hospital-General Campus,
203-311 McArthur Ave., Vanier, ON K1L 8M3.
Tel: (613) 744-8180 Fax: (613) 744-7982 E-mail: dr.gregoire@sympatico.ca

GUJRAl, N., Faculty of Pharmacy and Pharmaceutical Sciences,
#1100 Dent/Pharm Centre, University of Alberta, Edmonton, AB T6G 2N8
Tel: (780) 492-0547 E-mail: ngujral@pharmacy.ualberta.ca

GUPTA, M., 130 University Campus, Zeidler Ledcor Centre
University of Alberta, Edmonton, AB T6G2PA.
Tel: (780) 492-8245 Email: milligupta@gmail.com

GUTFREUND, K. S., Department of Medicine, 1-28B Zeidler Building,
University of Alberta, Edmonton, AB T6G 2X8.
Tel: (780) 492-0388 Fax: (780) 492-8143 E-mail: klaus.gutfreund@ualberta.ca

HABAL, F., Gastroenterology, Toronto General Hospital, 200 Elizabeth St.,
Office 9N977, Toronto, ON M5G 2C4. E-mail: flavio.habal@uhn.on.ca

HILZENRAT, N., Jewish General Hospital (Adult), 3755 Cote Ste Catherine,
Montreal, QC H3T 1E2.
Tel: (514) 340-8223 Fax: (514) 340-8282 Email: nir.hilzenrat@staff.mcgill.ca

HUNT, R.H., Division of Gastroenterology, McMaster University Medical Centre,
McMaster University, Room 4W8, 1200 Main St. W, Hamilton, ON L8N 3Z5.
Tel: (905) 521-2100 ext. 73219 Fax: (905) 521-5072 Cell: (905) 541-8777
GSM: 44-7785-260-430 E-mail: huntr@mcmaster.ca

JAYAKUMAR, S., 130 University Campus, Zeidler Ledcor Centre,
University of Alberta, Edmonton, AB T6G 2X8.
Tel: (780) 407-8822 E-mail: sjayakum@ualberta.ca

LAMOUREUX, E., Department of Pathology, University Clinic –
Montreal General Hospital.
Tel: 514.340.8222 Ext. 5481 Fax: (514) 340-8102 E-mail: esther.lamoureux@mcgill.ca

LEONARD, J., Cannon Falls Medical Center, 200 1st St SW,
Rochester, MN 55905 Tel: (507) 284-2511

LEVY, G.A., University Health Network, University of Toronto,
585 University Ave., 11-NCSB-1236, Toronto, ON M5G 2N2.
Tel: (416) 340-5166 Fax: (416) 340-3378 E-mail: glfgl2@attglobal.net

LI, Q., Department of Agricultural, Food & Nutritional Science,
University of Alberta, Room: 4-126E / 4-021 HRIF East, Edmonton,
AB T6G 2E1
Tel: (780) 492-4667 Fax: (780) 492-8855 Email: qunl@ualberta.ca

LILLY, L.B., University Health Network, 11-NCSB-1241, 585 University Ave., Toronto, ON M5G 2N2.
Tel: (416) 340-4629 Fax: (416) 340-3492 E-mail: les.lilly@uhn.on.ca

MA, M., Hepatology and Gastroenterology, University of Alberta,
8440-112th St., Edmonton, AB T6G 2R7.
Tel: (780) 492-8146 Fax: (780) 492-8148 E-mail: mang.ma@ualberta.ca

MACINTOSH, D.G., Gastroenterology), Dalhousie University,
Queen Elizabeth II Health Sciences Centre-Victoria General Site,
Centennial Wing, 1278 Tower Rd., Room 927, Halifax, NS B3H 2Y9.
Tel: (902) 473-3721 Fax: (902) 473-4406 E-mail: donald.macintosh@dal.ca

MASON, A. L., Division of Gastroenterology, 7-142J Katz Building,
University of Alberta, Edmonton, AB T6G 2X8
Tel: (780) 492-8176 Fax: (780) 492-1655 E-mail: andrew.mason@ualberta.ca

MAYRAND, S., Gastroenterology/Internal Medicine, MUHC-Montreal
General Hospital, D7 120-1650 av Cedar, Montreal, QC H3G 1A4.
Tel: (514) 934-8308 Fax: (514) 934-8375 E-mail: serge.mayrand@muhc.mcgill.ca

MERCER, C.D., General Surgery, Hotel Dieu Hospital, 166 Brock St.,
Kingston, ON K7L 5G2.
Tel: (613) 544-3400 Fax: (613) 546-4854 E-mail: mercerd@hdh.kari.net

MONTANO-LOZA, A. J., 120B-130 University Campus NW,
Ziedler Ledcor Centre, Edmonton, AB T6G 2X8.
Tel: (780) 248-1892 Fax: (780) 248-1895 E-mail: montanol@ualberta.ca

PARÉ, P., Professeur agrégé de clinique, Médecine, Université Laval,
CHAUQ-Hôpital du St-Sacrement, 1050 Chemin Ste-Foy, Quebec,
PQ G1S 4L8.
Tel: (418) 682-7511 ext. 4603 Fax: (418) 682-7855 E-mail: pierre.pare@cha.quebec.qc.ca

PATEL, D.G., Professor of Medicine, Gastroenterology, The Ottawa Hospital-
Civic Campus, A1-1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4501 Fax: (613) 761-5269 E-mail: dpatel@ottawahospital.on.ca

PATERSON, W.G., Gastroenterology/Internal Medicine, Professor of
Medicine, Biology and Physiology, Hotel Dieu Hospital, Queen's
University, 166 Brock St., Kingston, ON K7L 5G2.
Tel: (613) 544-3400 Fax: (613) 544-3114 E-mail: patersow@hdh.kari.net

RENNER, E. L., Director GI Transplantation, University of Toronto,
Toronto General Hospital/NCSB 11C-1238, 585 University Ave, Toronto, ON M5G 2N2.
Tel: (416) 340-4800 ext. 6821Fax: (416) 340-3126 E-mail: Eberhard.Renner@uhn.on.ca

ROMAGNUOLO, J., Division of Gastroenterology,
Medical University of South Carolina (MUSC), 96 Jonathon Lucas St.,
CSB #210, P.O. Box 250 327, Charleston, SC 29425.
Tel: (843) 792-9902 Fax: (843) 792-8395 E-mail: romagnuo@musc.edu

ROSTOM, A., Division of Gastroenterology, University of Ottawa, Ottawa
Hospital-Civic Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4603 Fax: (613) 761-5068 E-mail: arostom@ottawahospital.on.ca

ROWE, J.A., Assistant Professor of Department of Diagnostic Imaging, Dlhousie University, Rm 3226, Victoria
Building, Queen Elizabeth II Health Sciences Centre, Capital District Health Authority, 1276 South Park Street,
Halifax, N.S., B3H 2E8.
Tel: (902) 473-7770 Fax: (902) 473-2018 E-mail: jarowe@dal.ca

RUSSOS, P. G., Associate Professor of Medicine, University of Toronto,
Program Director, University of Toronto Division of Gastroenterology,
Director of Medical Informatics, University Health Network, Toronto
General Hospital, 9N-975, 200 Elizabeth St., Toronto, ON M5G 2C4.
Tel: (416) 340-5333 Fax: (416) 340-5335

SALOOJEE, N., Gastroenterology/Internal Medicine, The Ottawa Hospital-
General Campus, 501 Smyth Rd., Ottawa, ON K1H 8L6.
Tel: (613) 737-7777 ext. 76420 Fax: (613) 739-6151 E-mail: nsaloojee@ottawahospital.on.ca

SCULLY, L.J., Internal Medicine/Gastroenterology, The Ottawa Hospital-Civic
Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4830 Fax: (613) 761-5269 E-mail: lscully@ottawahospital.on.ca

SEKAR, A.S.C., Gastroenterology, Parkdale Medical Tower,
504-1081 Carling Ave., Ottawa, ON K1Y 4G2.
Tel: (613) 729-3179 Fax: (613) 729-1026 E-mail: arnisekar@rogers.com

SHAFFER, E.A., Division of Gastroenterology, Department of Medicine,
Faculty of Medicine, University of Calgary, 3330 Hospital Dr. NW,
Calgary, AB T2N 4N1. E-mail: shaffer@ucalgary.ca

SIS, B., Department of Laboratory Medicine and Pathology, 24-8440 112 ST NW,
5B4 University Hospital, Edmonton, AB T6G 2B7.
Tel: (780) 407-8132 Fax: (780) 407-3009 Email: bsis@ualberta.ca

SZILAGYI, A., Jewish General Hospital (Adult), 3755 Cote Ste Catherine,
Montreal, QC H3T 1E2
Tel: (514) 340-8223 Fax: (514) 340-8282 E-mail: aszilagy@gas.jgh.mcgill.ca

THOMPSON, W.G., Department of Medicine, University of Ottawa,
Chief of Gastroenterology, Ottawa Civic Hospital, 7 Nesbitt St.,
Ottawa, ON K2H 8C4.
Tel: (613) 761-4147 Fax: (613) 828-7300 E-mail: wgthompson@rogers.com

THOMSON, A.B.R., Division of Gastroenterology, Department of Medicine,
University of Western Ontario, London , ON E-mail: athoms47@uwo.ca

TURNBULL, G.K., Medicine, Dalhousie University,
1278 Tower Rd., Halifax, NS B3H 2Y9.
Tel: (902) 473-4140 Fax: (902) 473-4406 E-mail: turnbull@dal.ca

VANNER, S.J., Gastroenterology/Internal Medicine, Hotel Dieu Hospital,
166 Brock St., Kingston, ON K7L 5G2.
Tel: (613) 544-3400 Fax: (613) 544-3114 E-mail: vanners@hdh.ca

WATTERS, J.M., General Surgery, The Ottawa Hospital-Civic Campus,
1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4780 E-mail: jwatters@ohri.ca

WHITTAKER, J.S., Gastroenterology, 550-1144 Burrard St., Vancouver, BC V6Z 2A5.
Tel: (604) 683-6393 Fax: (604) 681-2421 E-mail: swhittaker@telus.net

WONG, F., The Toronto Hospital, General Division, 200 Elizabeth St.,
Toronto, ON M5G 2C4.
Tel: (416) 340-3834 Fax: (416) 340-5019 E-mail: florence.wong@utoronto.ca

754

Index

Note: Page numbers followed by f or t represent figures and tables respectively.,