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Nutrition and Hollow Organs of the Lower Gastrointestinal Tract

Ece A. Mutlu, Gökhan M. Mutlu, and Sohrab Mobarhan

Basic principles of nutrition in diseases of the small and large intestines are covered in this section. Often the disease processes are complex and result in challenges frequently requiring that nutritional treatment be individualized. Thus, consultation with a nutrition specialist is usually necessary and highly recommended.

Celiac Sprue (CS)

Definition and Epidemiology

Celiac sprue (celiac disease, gluten-sensitive enteropathy) is an allergic disease of the small intestine characterized by malabsorption of nutrients, a specific histological appearance on biopsy (Table 57.1), and prompt improvement after withdrawal of gluten (a water-insoluble protein moiety in certain cereal grains) from the diet. The disease is prevalent in almost every population, with higher numbers among people of northern European descent. In Europe, the prevalence is estimated to be 0.05 to 0.2%; however, the disease is underdiagnosed. When U.S. blood donors were screened using antiendomysial antibodies (AEA), which are serological markers with high specificity for CS, 1 in 250 were positive. The classic symptoms of the disease are diarrhea, flatulence, weight loss, and fatigue, although many patients without extensive small bowel damage may not have one or more of these symptoms. In fact, celiac disease patients may also be asymptomatic in terms of any GI manifestations, and may present with extraintestinal or malnutrition-related problems (such as miscarriages, osteoporosis with fractures, skin diseases, etc.) Clinical manifestations of the disease are given in Table 57.2. Patient populations at risk and their disease prevalence are given in Table 57.3.

Mechanisms

Gluten, the main allergen, is a protein found in wheat. The prolamin fraction of gluten is an alcoholic extract rich in proline and glutamine residues. This fraction is also termed gliadin, and certain amino acid sequences occurring in it (proline-serine-glutamine-

TABLE 57.1

Histological Features of Celiac Sprue (CS)

1. Loss of villi with resultant flat absorptive surface
2. Presence of cuboidal epithelial cells at surface
3. Hyperplasia of crypts, with increased mitotic figures
4. Increased intraepithelial lymphocytes
5. Increased cellularity in lamina propria

TABLE 57.2

Clinical Manifestations/Presentations of Celiac Sprue

Gastrointestinal	Extra-Intestinal
Diarrhea	Dermatitis herpetiformis
Steatorrhea/Weight loss	Amenorrhea/Infertility/Miscarriages
Nausea/Vomiting	Anemia (iron or folate deficiency)
GERD	Osteoporosis/Osteomalacia
Abdominal pain/Dyspepsia	Brittle diabetes
Bloating/Flatulence	Dementia
Occult blood in stool	Depression
Elevated transaminases	Neuropathy
Recurrent pancreatitis	Seizures
	Hyposplenism
	Headaches
	Hypoparathyroidism
	IgA nephropathy
	Malaise/Fatigue

TABLE 57.3

Patient Populations at Risk for CS

At Risk Population	Disease Prevalence
Family members of a patient with CS:	5-20%
Monozygotic twins	70-90%
Siblings with HLA DQW2 or HLA DR5/DR7	40%
First degree relatives	10-20%
Autoimmune thyroid disease	4-5%
Diabetes mellitus type I	2-5%
Ig A deficiency	15%
Sjögren's syndrome	15%
Down's syndrome	4-5%

glutamine and glutamine-glutamine-glutamine-proline) initiate the allergic reaction in CS. Many grains such as rye, barley and wheat also contain similar prolamin fractions, and are therefore toxic to CS patients (Figure 57.1). Taxonomy of common cereal grains and chemical names for their prolamin fractions are given in Figure 57.1.

In genetically predisposed individuals, the prolamin fractions from cereal grains bind a tissue autoantigen called tissue transglutaminase.[1] The bound complex is believed to initiate an autoimmune reaction leading to activation of intraepithelial T lymphocytes and formation of autoantibodies, resulting in destruction of small intestinal epithelial cells and the interstitium that make up the villus.

Tissue transglutaminase is normally found in the cytoplasm of the small intestinal epithelial cell, and its main function is to cross-link glutamine residues. *In vitro*, the enzyme preferentially acts on gluten, 35% of which is made up of glutamine, and renders it more susceptible to uptake and processing by the enterocyte. Tissue transglutaminase can also

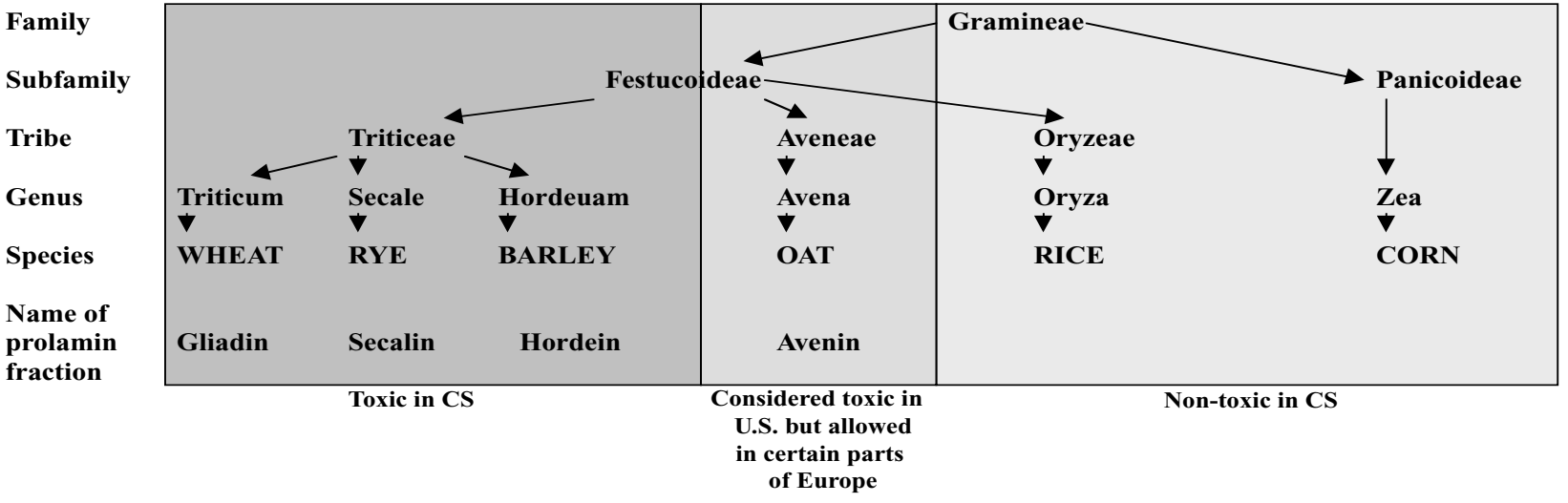

FIGURE 57.1
Taxonomy of grains.

TABLE 57.4

Pathogenetic Factors in Celiac Sprue

1. Dietary gluten
2. Genetic predisposition
   a. Association with HLA-DQw2, B8 and DR3
3. Autoimmunity
   a. Heightened gut permeability to macromolecules
   b. Increased T lymphocytes (esp. γΔ type) in lamina propria
   c. Increased humoral mucosal immune response
   d. Tissue transglutaminase
      i. Creation of new antigenic epitopes by binding gliadin
      ii. Deamidation of glutamine residues in gliadin, causing increased binding to HLA
4. Acute trigger factors
   a. Infection with viruses
   b. Acute inflammation due to food allergy, etc.
   c. Mechanical stress

deamidate glutamyl donor molecules, which can bind to celiac disease-specific HLA-DQ2 better than their non-deamidated counterparts.

How tissue transglutaminase and gluten come into contact is unclear. Postulated mechanisms include exposure during mechanical stress, inflammation, infection, or apoptosis. For example, instigation of tissue injury by infection with adenovirus 12 has been hypothesized to cause release of tissue transglutaminase into the extracellular environment where it links with gluten. Supporting this hypothesis, Kagnoff et al.[2] have shown that a particular portion of the E1B protein of adenovirus 12 and alpha-gliadin are homologous, and 89% of patients with CS have evidence of prior exposure to this virus. Others propose that gluten is inadequately digested and toxic fractions accumulate. Subsequent sampling of the intestinal milieu leads to presentation of the gliadin peptides on antigen presenting cells within the cleft of the HLA-DQ2 molecules carried by susceptible individuals. Various hypotheses and factors important in the pathogenesis of CS are given in Table 57.4.

Effects on Nutritional Status

CS can profoundly affect nutritional status, leading to steatorrhea, weight loss, and many micronutrient deficiencies, although about half of adult patients present with rather subtle clinical signs of malnutrition, as the disease can be patchy, and the extent of involvement of the small intestine varies from person to person. The degree of malnutrition is positively correlated with the presence of symptoms; asymptomatic patients are less malnourished than symptomatic ones (31 versus 67%).[3] CS patients tend to have lower body fat, bone mass, and lean body mass compared to healthy controls. Total body fat can even be decreased significantly in asymptomatic cases with latent sprue.[4] Laboratory studies show that albumin, triglycerides, and hemoglobin are typically below normal. Anemia is frequent in both overt and latent CS, and may be due to iron, folate, or vitamin B_{12} deficiencies resulting from malabsorption and/or bacterial overgrowth. Micronutrient problems such as low calcium, potassium, magnesium, copper, zinc, and selenium, and vitamin K deficiency have been reported. Additionally, vitamin E deficiency has been linked to the neurological symptoms of CS. Of utmost importance, patients with symptomatic as well as latent CS may have osteomalacia and/or low bone mineral density[5] partly as a result of vitamin D and calcium deficiency, and these need to be supplemented to prevent osteoporosis. There is no correlation between clinical or biochemical abnormalities and bone mineral density, so supplementation with regular screening should be undertaken in all patients.

Diet in Celiac Sprue

The Gluten-Free Diet

CS patients need to avoid foods that contain certain cereal grains. For medical purposes, such a diet is termed a gluten-free diet (GFD). In general, the oryzeae or the tripsaceae such as rice, corn, and maize are safe because the protein fractions of these grains are significantly different from gliadin, due to their different taxonomy, shown in Figure 57.1. Basic principles of the GFD are given in Table 57.5.

Caution should be exercised when the word "gluten" is used to select foods, as it has different meanings to different people. Bakers typically use it to mean the sticky part of grains, whereas chemists only refer to wheat-derived protein fractions, and use the chemical names given in Figure 57.1 for other cereal grains. Therefore, patients are encouraged to ask, "Is this food free of wheat, rye, barley, oats, etc., and ingredients derived from grains?" rather than, "Is this a gluten-free food?."

Unfortunately, many dietary additives exist in processed foods containing hidden ingredients that are derived from cereal grains; therefore, compliance with a truly GFD diet is difficult. A simple watch list for some of these ingredients is given in Table 57.5, Item 3. Chemicals/fillers added to nonfood items such as vitamins and pills may also be sources of gluten. Moreover, food-processing elements, which need not to be reported on food labels, may use grains. Hence, patients are encouraged to consult a dietitian experienced in GFD with questions, as well as to join professional societies such as The Celiac Sprue Association, U.S.A.

Manifestations of the diseases responsive to GFD are given in Table 57.6. Numerous studies show that GFD is not only essential in controlling GI symptoms, but also prevents complications.

Osteopenia and osteoporosis are common, and can result from vitamin D and calcium malabsorption as well as secondary to hypoparathyroidism from hypomagnesaemia.[6] GFD leads to increases in bone mineral density, with the greatest benefit in the first year of treatment,[7-10] but normalization may not occur even on GFD.[10] In a study of 65 patients with CS on GFD, up to 50% had a T score of less than –2 on dual energy x-ray absorptiometry.[11]

There is a two- to threefold relative increase in the risk of cancer among patients with CS.[12,13] Specifically, T-cell lymphomas of the small intestine, adenocarcinoma of the small intestine, cancers of the mouth, nasopharynx, and esophagus are more common in CS.

TABLE 57.5

Principles of the Gluten-Free Diet (GFD)

1. Avoid the following grains: wheat, rye, barley, oat, spelt (dinkel), kamut, buckwheat
2. Avoid the following grain based products: bulgar*, couscous*, wheat starch, wheat germ, semolina*, durum*, bran, oat bran, germ, graham flour
3. Avoid potentially grain based products or additives: malt**, malt flavoring, malt extract, malt syrup, food starch (edible starch)***, icing sugar****, soy sauce*****, filler+, gum base, oat gum, cereal binding, white vinegar*****, hydrolyzed vegetable protein or hydrolyzed plant protein
4. Avoid sauces, salad dressings, and fat substitutes as these may typically contain grain-derived products.
5. Avoid grain-based alcohol such as beer or alcoholic extracts of grains.
6. Corn and rice are the only allowable cereal grains.
7. All fresh vegetables and fruits are allowed.

* derived from wheat
** may be derived from barley
*** may be derived from wheat
**** contains 5% wheat starch
***** may contain wheat or barley
+ found frequently in medications and vitamins

TABLE 57.6

Manifestations of CS Responsive to GFD

1. Gastrointestinal symptoms
a. Diarrhea
b. Malbsorption
2. Osteopenia/Osteoporosis
3. Anemia
4. Dermatitis herpetiformis
5. Depression
6. Increased risk of malignancy
7. Amenorrhea/Infertility/Spontaneous abortions

Malignant complications correlate with GFD; in patients who have been on GFD for five years or more, malignancy risk reverts back to that for the general population.[13,14] For those on a reduced gluten or normal diet, the risk for non-Hodgkin's lymphoma and cancers of the mouth, pharynx, and esophagus is 78-fold, and 23-fold higher compared to the general population.[13]

The time to respond to GFD clinically varies, depending on the severity of disease. A prompt improvement in symptoms is expected within days to a few weeks. Patients with milder disease in biopsies tend to respond sooner than those with villus atrophy, in whom resolution of symptoms may take up to several months. Still, normalization of biopsy samples when total villus atrophy is present has been reported incomplete even after two years.[15] Dermatitis herpetiformis takes longer to resolve with GFD than other symptoms (on average two years), and older patients take longer to respond than younger ones.

What to Do in the Patient Who is Unresponsive to a GFD?

From a dietary standpoint, careful review of the patient's diet for hidden sources of gluten is suggested. The most common causes of GI symptoms in such patients are bacterial overgrowth, development of other autoimmune diseases, and a new onset of microscopic/collagenous colitis found in 5% of patients with CS. Treatment of bacterial overgrowth with antibiotics may be beneficial.[16] Complications of CS such as development of T-cell lymphoma, adenocarcinoma, and collagenous sprue should also be investigated.

Exocrine pancreatic insufficiency due to impaired cholecystokinin-pancreozymin release from abnormal mucosa has been reported, suggesting a beneficial role for pancreatic enzyme supplements.[17,18] In fact, mild to moderate pancreatic insufficiency with subnormal levels in one or more pancreatic enzymes was found in 29% of patients with CS in one study, and the presence of insufficiency did not seem to correlate with overall nutritional status.[19] A prospective, double-blind, randomized study of adolescents has shown improvement in anthropometric variables as well as weight gain with enzyme supplementation.[20]

Searches for dietary antigens other than gliadin have shown usefulness to an elimination diet in 77% of patients in one study.[21] This elimination diet excluded foods containing natural salicylates, amines and/or glutamine, food colorings, preservatives, monosodium glutamate, lactose and/or dairy products, soy, and millet-containing foods.

Patients in whom symptoms persists are considered to have "refractory sprue" upon exclusion of other diagnoses. These patients may benefit from corticosteroids,[22] azathioprine,[23] or cyclosporine.[24] Zinc-deficient patients with refractory sprue may respond to zinc supplements,[25] although this issue is controversial.[26]

Is There a Safe Amount of Gluten that CS Patients May Consume?

The amount of gluten required to initiate CS is unknown. One study suggests that at least 10 g-gluten challenge leads to relapse of disease within seven weeks,[27] although there is

no consensus in this regard. Diets recommended by professional societies in the U.S. do not allow any gluten, whereas the Codex Alimentarius Commission of the Food and Agricultural Organization of the United Nations (FAO) and the World Health Organization (WHO) permit a gluten-free label on foods that contain up to 0.3% of protein from toxic grains. Most of this protein comes from wheat starch or malt.

Wheat starch (that only contains 0.75 mg/100 g gliadin) is not tolerated well, and its withdrawal from the diet results in marked improvement of intestinal symptoms and dermatitis herpetiformis.[28] In a recent study examining patients who are symptomatic despite the GFD as defined by FAO/WHO standards, conversion to a no-detectable gluten diet resulted in complete resolution or reduction of symptoms in 23 and 45% respectively.[29] Based on these results, there is no safe amount of gluten in the diet.

Can CS Patients Eat Oats?

Evidence that oats may not be harmful to CS patients dates back to the 1970s, when Dissanayake, Truelove, and Whitehead administered 40 to 60 g of oats to four CS patients for one month and showed no damage to the small intestinal mucosa.[30] Several investigators claim that oats, which taxonomically belong to a different subclass in the cereal grains, the aveneae, do not elicit the immune reaction seen with the ones in the triticeae tribe; oats have a lower content of proline, which is abundant in the toxic amino acid sequences (proline-serine-glutamine-glutamine and glutamine-glutamine-glutamine-proline) of prolamin fractions. Also, these sequences occur fewer times per molecule of oat avenin as opposed to wheat prolamin.[31] Whether such lower amounts are enough to elicit the autoimmune reaction of CS or whether there is a certain safe level of oat consumption is unclear. *In vitro* investigations show that antibodies from sera of patients with CS and dermatitis herpetiformis can react against oat avenin, but the significance of this finding is questionable, because similar immunoreactivity against corn has also been demonstrated.[32]

Two small cohort studies with CS and dermatitis herpetiformis patients have shown no rise in antibody titers and no clinical or histological deterioration when oats are given 50 g/day and 62.5 g/day, respectively.[33,34] In the largest randomized placebo-controlled study to date, newly diagnosed European patients and ones in remission on GFD were studied for 12 and 6 months, respectively.[35] The patients were not blinded, although the investigators were. Consumption of 50 g of oats daily did not cause any clinical relapse or histopathological worsening in the established patients with CS, nor did it prevent clinical or histological healing in newly diagnosed cases. The authors concluded that small to moderate amounts of oats can be included in a GFD, and may improve poor compliance with the diet. Despite the well-design of this study, long-term evidence regarding the safety of oats is lacking. Considering crop rotation and lack of specified mills for oats in the U.S., addition of oats to GFD cannot be recommended at this time.

Should CS Patients Also Avoid Lactose?

Lactase, the enzyme needed for digestion of lactose, is located at the very tip of the brush border. As a result of damage to the villi, the levels of lactase are assumed to be lower in most acutely ill patients with CS. Therefore, most professionals advocate a lactose-free diet at the beginning of treatment with a GFD until resolution of symptoms. This is especially true for patients with severe disease, requiring corticosteroids. No controlled studies have been done examining the utility of a lactose-free diet in CS. Long-term avoidance of lactose is not appropriate, considering the high incidence of osteopenia among CS patients.

Does Breastfeeding Prevent Occurrence of CS?

The incidence of CS is increased in the relatives of patients. The relative risks for family members of CS patients are given in Table 57.3. Retrospective studies have shown that

TABLE 57.7

Nutritional Tips for CS Patients

1. Avoid lactose (mainly milk and dairy products) in acute disease
2. Follow a gluten free diet (Table 57.5) at all times:
   a. Read food labels
   b. Ask about grains in foods and medications
   c. Avoid all foods if it is not certain that they do not contain the restricted grains
   d. Select plain meats, fresh fruits, and vegetables when eating outside of the home if not sure
   e. Record weight and symptoms, and keep a food diary until symptoms resolve on the GFD
3. Avoid foods that initiate/exacerbate symptoms as they may contain hidden sources of grains or other food allergens
4. Consult an experienced dietitian with questions
5. Report persistent symptoms promptly
6. Join support groups for people with CS

relative risk of CS development is fourfold less in siblings of Italian children with CS if they are breastfed for over 30 days.[36] Similar findings showing a protective effect of breastfeeding has been confirmed in Tunisian children.[37] This effect may be correlated with duration of breastfeeding, and appears independent of the delays in introduction of wheat and grain products into an infant's diet.[38] Age at gluten introduction seems to be a separate factor. Epidemiological evidence links increasing incidence of CS in Sweden, as opposed to Denmark, to early- and high-level introduction of gluten into infant feedings.[39] However, case control studies have not yet confirmed these results.[40] Presently, this topic needs further study. Nutritional tips for CS are given in Table 57.7.

Inflammatory Bowel Disease (IBD)

Definition and Epidemiology

Inflammatory bowel disease is an idiopathic chronic inflammatory disorder of the gastrointestinal system. The two main forms of the disease are Crohn's disease (CD) and ulcerative colitis (UC). The main differences of these diseases are shown in Table 57.8.

Mechanisms

Various factors and mechanisms important in the pathogenesis of IBD are listed in Table 57.9. Most recently, certain genetic foci associated with IBD have been discovered, and it

TABLE 57.8

Differences between UC and CD

	UC	CD
Clinical	Bloody diarrhea is main symptom	Obstruction, fistulae, perianal disease may be present
Site of involvement	Rectum extending proximally into colon as a continuum	Any part of the GI tract Normal tissue between areas of involvement (i.e., skip areas)
	Small bowel normal	70% small bowel involvement
	Only mucosal involvement	Involvement of the entire bowel wall
Pathological appearance	No granulomas	Presence of granulomas
Prognosis/recurrence	Can be cured with colectomy	Cannot be cured with surgical resection

TABLE 57.9

Factors Important in the Pathogenesis of IBD

1. Genetic predisposition
2. Environmental factors (e.g., smoking, urban lifestyle, etc.)
3. Dietary factors
4. Infectious agents
a. Mycobacteria
b. Measles virus
5. Immune reactivity
6. Psychosocial factors and stress

is hypothesized that environmental factors in susceptible individuals ultimately initiate the inflammatory process leading to disease. Environmental factors include diet and dietary antigens as well as the bacterial flora of the intestines.

Effects on Nutritional Status

Malnutrition is common in IBD; however, there is an important difference between CD and UC. CD usually leads to chronic malnutrition that develops insidiously over long periods of time, whereas in most cases, UC causes acute reductions in weight during flareups of disease. Up to 85% of patients hospitalized with IBD and about 23% of outpatients with CD have protein-energy malnutrition.[41] Stable patients with the disease tend to have a normal fat-free mass but low fat stores.

The causes of malnutrition in patients with IBD are multifactorial, and are given in Table 57.10. There is an increase in the resting metabolic rates in active IBD, but mean increases are modest (19% in active UC,[42] 12% in active CD[43]) when compared to the calculated ones from the Harris Benedict Equation, or to controls. Total energy expenditures, however, are comparable to healthy people.[44] Most stable outpatients with IBD do not have increased energy expenditures either.[45] One exception is underweight individuals (body weight <90% of ideal)[45,46] who may represent a special subgroup with specific metabolic abnormalities different than the rest. Interestingly, stable patients with CD who have decreased fat stores but a similar fat-free mass to healthy controls or UC patients, have enhanced utilization of lipids and diet-induced thermogenesis.[47,48] A worse subclinical disease might be the cause in these patients, as increased lipid oxidation is seen with active disease and its level correlates with disease activity.[43]

TABLE 57.10

Causes of Malnutrition in IBD Patients

1. Reduced dietary intake
a. Anorexia to avoid symptoms
b. Restricted diets
c. Drug-induced taste alterations
2. Maldigestion and malabsorption
a. Inadequate mucosal surface
b. Bile salt malabsorption from ileal disease
c. Bacterial overgrowth
d. Drug induced
3. Increased requirements
a. Inflammatory catabolism
b. Drug-induced nutrient wasting
4. Exudative protein losses from inflamed intestine or fistulae

TABLE 57.11

Micronutrient Deficiencies in IBD

	% Prevalance in:	
Micronutrient	**UC**	**CD**
Iron	81	39
Folic acid	35	54-67
Vitamin B_{12}	5	48
Potassium		6-20
Calcium		13
Magnesium		14-33
Vitamin A	26-93	11-50
Vitamin D	35	75
Zinc		40-50
Selenium		35-40

Fecal energy and protein losses in IBD are significant in active IBD, but most patients compensate by increased food intake. Generally, patients on corticosteroids are also in positive energy balance, possibly due to the appetite stimulant properties of these drugs.[49] Yet, attention should be paid to the provision of adequate protein to meet increased protein need by the patient with active IBD, especially in malnourished patients who may require as much as 2 g/kg/day of protein.[50]

Food intolerances are twice as common among IBD patients as in the general population.[51] These intolerances are commonly towards corn, wheat, cereals, cruciferous vegetables, and milk, although intolerances to foods such as rice or even tap water have been observed.

In patients without obvious malabsorption, food intolerances together with less hunger, decreased appetite, and fewer sensations of pleasure related to eating lead to significantly reduced food intakes.[52] This is the major cause of weight loss in patients with IBD.[52] In patients without other objective evidence of active inflammation, weight loss should not be attributed to IBD, but rather close attention should be paid to the patient's food intake.

Patients with IBD commonly have many micronutrient deficiencies, as shown in Table 57.11. Low levels of zinc and selenium that are cofactors for oxidant-protective enzymes and low antioxidant vitamins (A, E, and C) have been implicated in worsening of the disease course as well as contributing to the high rate of carcinogenesis among IBD patients.

Osteopenia, a well-recognized complication of IBD, is widespread among both adult and pediatric patients[53] and may occur independent of steroid use. Both osteopenia and osteoporosis have been linked to vitamin D and calcium deficiencies, and supplementation has been beneficial in treatment of these disorders.

Diet in IBD

Diet as a Potential Cause of IBD

Epidemiological evidence suggests that the incidence of Crohn's disease (CD) has been increasing over the last half century, while that of ulcerative colitis (UC) is declining, especially in developed countries. Moreover, migrant populations of Asians into England, or of European Jews into the U.S., have a much greater increase in the incidence of CD compared to their counterparts living in their native countries. Assuming that the migrants and natives have similar genetic pools, the increase has been attributed to environmental factors. Strikingly, a higher incidence of CD in urban areas as opposed to rural ones further suggests environmental factors at play. Among these factors, diet is important.

Pre-Illness Diet Factors and Dietary Habits of Patients with IBD

Many studies on dietary factors in the development of IBD and the roles of many types of food (such as refined sugar, cereals, fiber, and dairy products including milk) have been undertaken.

In general, patients with IBD tend towards higher intake of sugar compared to controls,[54,55] and this trend specifically reaches statistical significance for CD[54,55] in most studies, and for UC in one.[56] Fruit, vegetable, and fiber consumption, on the other hand, was much lower in IBD in these studies. One study in the Japanese population confirmed the lower intakes of vegetables and fruits among IBD patients, and a Westernized diet increased the risk for UC.[57] These findings among IBD patients are not surprising, as they may represent an adaptation to the disease process rather than the cause of IBD.

Realizing this pitfall, in some studies only patients who have recent exacerbation of IBD were questioned about their diets. Such studies also confirmed that there is higher intake of sugars among CD patients but not UC ones.[58-64] In one of these, deleterious effect of increased intake of sugars was only seen with sucrose, but not with lactose or polysaccharides.[58] IBD patients also consume more fat prior to onset of disease.[58] One epidemiological study suggests that IBD is related to increased n-6 polyunsaturated fatty acid and animal protein intake.[65]

Does Milk Cause IBD? Should Patients with IBD Avoid Milk?

The role of milk in initiating or worsening IBD is debatable, and whether lactose intolerance is more common in IBD is controversial. Even among IBD patients who are not lactose malabsorbers, elimination of milk from the diet leads to improvement in diarrhea in 1/5 to 1/4 of the cases with UC, and in 1/3 of the patients with CD.[66,67]

Although no clear-cut explanation for this exists, morphological changes in small intestinal mucosa are well documented in CD and UC.[68,69] The extent to which these changes are related to decreased food intake or starvation as a result of disease symptoms is unknown. Nevertheless, in CD, improvements related to a milk-free diet are not attributable to changes in brush border lactase levels.[70] In UC, measurements of intestinal lactase have shown that deficiencies of lactase are real during active disease, but lactase deficit is not necessarily more frequent in the active phase compared to inactive.[71]

This raises the question of whether milk itself is an allergen. One group of studies has searched for humoral immune responses to milk proteins. Antibodies to milk proteins can be readily detected in sera of IBD patients,[72] but their levels may not be increased[73,74] nor are they particularly common.[75] Some investigators have correlated antibody response against milk to disease activity in CD but not in UC.[76] However, disruptions of the intestinal barrier as a result of inflammation can easily lead to such antibody formation, making it a secondary phenomenon rather than the cause of disease. Other studies have directly looked at the effects of a milk-free diet. In one, elimination of milk from the diet decreased relapses of UC when patients were followed up to one year subsequent to treatment with steroids[77] even though strict statistical comparisons between treatment and control groups were not undertaken. In another small study, 40% of IBD patients without lactose intolerance improved.[66] Allergy to cow milk may play a role in initiating or perpetuating inflammation in IBD in a subset of patients, although no evidence clearly establishes milk as an allergen.

Milk may also modify the intestinal flora, causing harm to individuals genetically susceptible to IBD, or to IBD patients. Supporting this hypothesis, lack of breastfeeding has been an independent risk factor for childhood CD,[78] but not UC.[79]

Is IBD Caused by Allergy to Foods?

In a subset of patients who respond to elimination diets, IBD may be caused by allergy to a specific food item. However, such patients constitute a very small minority and may represent cases with an allergic colitis that is misdiagnosed as IBD. Further studies are needed to answer this question.

Dietary Treatment for IBD

Energy and Protein Requirements in IBD

The Harris Benedict equation is useful in calculating the energy requirements of IBD patients. Active disease may increase calculated requirements up to 20%. Fecal losses of protein are the norm in active disease; therefore, patients should be given or encouraged to consume at least 1.5 g/kg of protein.

Effects of Diet Counseling

Individualized dietary counseling for six months can lead to significant decreases in the CD activity index, the need for medications such as prednisone, days spent in the hospital for acute exacerbations, and number of days lost from work.[80] Counseling can also lead to increased incidence of disease remission, with beneficial effects persisting up to one year, and is useful in both active and inactive disease.

Unproven Diets

High Fiber Diets that Restrict Sugar or Provide Unrefined Carbohydrates

Investigators have studied the impact of a diet with little or no sugar, rich in unrefined carbohydrates and fiber on IBD. In one open-label study of CD patients and matched controls, hospital admissions were significantly fewer and shorter in the treatment group.[64] Subjects were given over 30 g of fiber/day on average, with no adverse effects seen in the patients with strictures. In a larger, better-designed, controlled, multicenter trial with CD, the diet intervention group did not have a clinically different course than the group consuming a low-fiber, unrestricted sugar diet.[81]

Low Residue Diet for Active CD

A study of patients with active nonstenosing CD compared a low-residue diet with an ad-lib diet.[82] There were no differences in the incidence of poor outcomes such as need for surgery, hospitalization, prolonged bedrest, partial obstruction, or new inflammatory mass.

The Simple Carbohydrate Diet

Patients are resorting to diet therapies because of the many side effects of immunosuppressive medications used in treatment of IBD and their lack of effectiveness in a significant number of cases. There is a growing body of anecdotal evidence towards the efficacy of various diets used by patients. One very popular example is the simple carbohydrate diet (SCD) pioneered by Dr. Haas and currently advocated by Elaine Gottschall, whose son has been afflicted with UC.[83] The diet is based on avoidance of all complex sugars and grains, is gluten-free, and is devoid of all additives/preservatives. With a few exceptions, only fresh food is allowed, and it is cooked well to promote easy digestion. The principles of the diet attempt to generate an "elemental carbohydrate diet." Although elemental diets work in IBD, polymeric enteral formulas have been found to be just as effective in one-to-one comparisons. Moreover, many of the elemental formulations do, in fact, contain

polymeric carbohydrates, refuting the possibility that taking in only simple carbohydrates will be successful. To date, the SCD diet has not been tested scientifically; therefore it cannot be advocated for general use. If it is proven effective after objective scientific evaluation, this may be based on features other than its "simple carbohydrates." For the patient who wishes to stay on the SCD diet, adequate macro- and micronutrient intake should be supervised by an experienced dietitian.

Elimination Diets

Report of food intolerances by IBD patients have led to investigations into elimination diets as a potential therapy. In an uncontrolled trial, 66% of CD patients were able to find a nutritionally adequate diet after elimination of various foods.[84] More than half of these patients needed elimination of more than one or two foods. The relapse rate was 33% at the end of the first year on the diets, with annual averages of about 14% within the first three years. A controlled trial by the same investigators showed that 7/10 patients in the treatment group remained in remission after three months, as opposed to all patients relapsing in the control group given an unrefined carbohydrate fiber rich diet.[84] Unfortunately, these beneficial results have not been confirmed with better-designed studies to eliminate bias. In fact, in a study of 42 eligible CD patients put into remission with elemental diet, 33% dropped out of the study; 19% did not identify food intolerance, and 48% did.[85] Among this 48%, food sensitivity was confirmed in half, in open-challenge with the item, and this was reproducible in only three patients on double-blind challenge. These findings suggest that elimination diets are of little help in the day-to-day treatment of IBD.

Growth Hormone and High-Protein Diet

The effects of high-protein diet versus glucocorticoids on the course of active CD was considered in a small study of pediatric patients. No significant dissimilarities between the two treatment groups in terms of improvement of pediatric Crohn's Disease activity index (CDAI) or laboratory parameters at two weeks were observed, although the study may not have had adequate power to detect any differences. In a followup of 1.3 years, patients given steroids tended to relapse more than the diet group.[86]

High-protein diet and growth hormone also have been shown to enhance adaptation of the small intestine after massive resection[87] and to improve protein absorption and reduce stool output and requirements for hyperalimentation in short bowel syndrome when used together with glutamine.[88] A pilot study of high-protein diet (protein intake = 2 g/kg/day) in conjunction with growth hormone injections (loading dose 5 mg/day for one week, maintenance 1.5 mg/day for four months) in moderate-to-severe CD patients undergoing conventional treatment has been studied in a double-blind and placebo-controlled fashion. Although the study is limited because of a small number of patients and does not indicate the percentage of patients entering remission, a significantly lower score of CDAI was seen in the treatment group.[89] This effect may be a result of increased amino acid uptake and electrolytes, increased intestinal protein synthesis, and/or decreased intestinal permeability in response to growth hormone. Further studies are needed before this treatment is applicable in clinical practice.

Fish Oils (Omega-3 fatty acids)

Omega-3 fatty acids such as eicosapentaenoic acid and docosahexanoic acid have been shown to inhibit production of leukotriene B_4, a major neutrophil chemo-attractant in IBD. In two trials with active UC patients, oral fish oil decreased steroid requirements and improved histology.[90,91] In another study of patients with moderate UC, decrease in disease activity was seen, although no improvement was noted in histology or leukotriene B_4 levels.[92] In UC, no beneficial effects of fish oil in maintenance of remission were seen.[90,93]

In CD, intravenous administration of eicosapentaenoic acid increases the ratio of leukotriene B_5: leukotriene B_4.[94] A one-year study in CD patients has shown reduced rates of relapse while on high doses of n-3 fatty acids (= 2.7 g/day), given as nine capsules a day. Compliance can be difficult with this regimen because of the large number of pills, and because some patients report a fishy odor at this dosage.

Capsaicin

Capsaicin, found in peppers, worsens colitis in IBD animal models by interfering with sensory neuroimmunomodulation.[95] No data exists in humans.

Short Chain Fatty Acids (SCFAs)

SCFAs are produced in the colon by fermentation of fiber or undigested starch by colonic flora, and represent the primary energy source of colonic cells. Small open-label trials of butyrate, a SCFA, given as an enema to patients with left-sided UC, have shown rates of remission similar to treatments with steroids and mesalamine.[96-99] The expense and the pungent smell of SCFA enemas precludes their clinical use; oral precursors of SCFAs are being developed. In animal studies, pectin increases SCFAs and leads to reduction of inflammation and enhancement of repair.[100]

Gut Microflora/Probiotics/Prebiotics

A large body of research indicates that the intestinal flora may be proinflammatory in IBD. This may explain why antibiotics that alter the flora, such as fluoroquinolones or metronidazole, or diversion of the fecal stream with an ostomy, are utilized in the treatment of IBD. The proinflammatory effect of the flora may be a result of expansion of harmful colonies of normal gut microorganisms in the presence of certain lumenal conditions such as an acidic pH, etc. Therefore, novel probiotic therapies that administer "good colonies (non-inflammatory)" of gut bacteria, which compete with "bad colonies," have been developed for treatment of IBD. One of these, *E. coli* strain *Niessle 1917* most recently has been shown to be as effective as conventional treatment with 5-ASA drugs in the maintenance of remission in UC.[101] Another probiotic preparation containing 5×10^{11} composed of four strains of lactobacilli, three strains of bifidobacteria and one strain of Streptococcus salivarius can prevent recurrence of pouchitis, (inflammation of the ileal pouch anastomosed to the rectum in patients who have undergone colectomy for UC), in a nine month follow-up period.[102] A different approach has been the use of prebiotics, nondigestible food substances that promote only the growth of a defined subset of good bacteria. Certain foodstuffs or their components have been found to be prebiotics (e.g., fructo-oligosaccharides and oats) that can profoundly influence the gut microflora, favoring expansion of good organisms like lactobacillus. Although no controlled studies with these substances exist in humans, a pilot study of patients with IBD has reported increases in favorable intestinal flora as well as SCFA.[103]

Medium-Chain Triglycerides (MCTs)

Foods rich in medium-chain triglycerides are readily absorbed, and enhance kcaloric intakes in malabsorptive states like IBD.

Enteral Nutrition and IBD

Primary Therapy

Many different formulations have been used for enteral nutrition in IBD. Polymeric formulas usually have starches, complex protein, long-chain triglycerides, and MCTs.

Semielemental formulations contain oligosaccharides, peptides, and MCTs. Elemental formulations typically contain predigested nutrients such as amino acids and glucose.

In active CD, comparison of elemental/semielemental diets with corticosteroids have shown equal efficacy in achieving short term remission (≤ 3 months) in the range of 70 to 80% in individual studies,[104-106] but a meta-analysis indicates that steroids may be more effective.[107] Long-term effects of enteral diets are less well known, although percentage of patients in remission at one year ranges from 9 to 56%.[105,106,108] This rate is not significantly different when elemental diets are compared with polymeric or semi-elemental formulations in most studies.[107,109] Elemental diets are poorly tolerated because of their smell/taste, complications such as diarrhea, and high costs. Therefore, polymeric formulations should be favored. Furthermore, relapse rates are generally higher with elemental diets as opposed to conventional therapy;[110] therefore, enteral nutrition as primary therapy should be attempted only in selected cases.

Investigators have found that CD patients with severe disease[111] and/or CDAI >450[112] and patients with colonic disease together with a fever[113] are less likely to respond to enteral nutrition therapy. In one study, the initial response rates were 38 versus 76% for CD patients with moderate disease, as opposed to patients with severe inflammation.[111] Studies with UC reveal no benefit from enteral nutrition for induction of remission.[114]

Comparison of hyperalimentation with enteral nutrition in CD has shown no superiority of parenteral nutrition.[41,109,115] Given the multiple potential side effects of parenteral nutrition, enteral therapy should be used whenever possible.

Parenteral Nutrition and IBD

Preoperative

Parenteral nutrition decreases postoperative complications only in severely malnourished patients with IBD. In one study, therapy duration of at least five days was required to see any beneficial effect.[116]

Primary Therapy

Randomized prospective studies have shown a response rate to parenteral nutrition in the 30 to 50% range in acute UC, but no significant differences over placebo have been demonstrated.[117-120] Furthermore disease-free maintenance rates on total parenteral nutrition (TPN) have been poor, and complications requiring surgery may be higher; therefore, there is no role for TPN as primary therapy of UC.[117-120]

In retrospective and prospective analyses in CD, parenteral nutrition can induce remission in 70 to 100% of patients refractory to conventional treatments,[114,115,117,118] but in at least one prospective study, 60% relapse rate is seen within two years.[121] This rate is four times higher than historical controls treated with surgical resection. Therefore, consideration of parenteral nutrition is recommended only in patients who are malnourished and have extensive disease precluding surgical treatment. Given the many complications of parenteral nutrition, this treatment should be a last resort, after exhaustion of other therapies.

Micronutrients

Antioxidants

Lower levels of antioxidant vitamins such as vitamin A, E, C, and beta-carotene have been shown in both sera and colonic tissue of patients with IBD when compared to healthy controls.[122,123] In one study, vitamin C level also correlated with disease severity.[122] Vitamin C can especially be low in patients with fistulous tracts.

Animal studies suggest that antioxidant supplementation over and above corrections for deficiency states may ameliorate colitis; however, no randomized placebo controlled trials have been performed in humans.

Calcium/Vitamin D

Low levels of vitamin D are found in 75% of patients with CD and 35% of patients with UC.[109] Low levels also correlate with disease activity in undernourished CD patients.[124] Of such patients, 45% have osteoporosis.[125] Therefore, supplementation of vitamin D and calcium is essential for the prevention of osteopenia/osteoporosis in IBD. Smoking also independently increases the rate of osteoporosis, and should be avoided.

Folate

In retrospective analyses, folate supplementation has been shown to reduce incidence of dysplasia and cancer in patients with UC.[126,127] Folate requirements in IBD are increased due to anemia and medications such as azathioprine, 6-mercaptopurine, and sulfasalazine; therefore supplementation is recommended in almost all patients.

Zinc

Zinc deficiency is especially common among patients with fistulous disease, and has been implicated as a cause for poor wound healing in these patients.[128]

Vitamin B_{12}

Deficiency of vitamin B_{12} occurs as a result of ileal involvement or resection as well as bacterial overgrowth in CD. All patients with CD should have supplementation either nasally or as monthly injections, because oral absorption is inadequate. Recently, sublingual administration of two over-the-counter vitamin nuggets (1000 μg/nugget) daily for seven to ten days to a small group of patients with B_{12} deficiency has been reported to be effective in raising blood levels. This latter route requires further study.

Specific Situations

Obstruction

Patients with intermittent obstruction are advised to consume a low-residue diet, although no definite data exists.

Fistulae

Postoperative fistulae may respond to TPN, but CD fistulae are less likely to close and frequently reopen promptly after food intake is resumed.[129,130] Similar results are seen with elemental diet.[111,113,131,132] In the era of effective anti-tumor necrosis factor therapies, TPN cannot be recommended as first-line therapy for fistulae in CD.

Severe Diarrhea and Antidiarrheals/Pectin

Diarrhea can be disabling for patients with IBD, and many require antidiarrheals such as Loperamide or Lomotil. These agents induce their effects by diminishing GI motility by binding opioid receptors in the GI tract, and therefore have been implicated in the pathogenesis of IBD complications such as toxic megacolon. Thus, caution should be exercised when using these, and for severely symptomatic patients without any obstruction, antidiarrheals such as Kaopectate, that bind excess liquid in the lumen, should be tried.

TABLE 57.12

Nutritional Tips for IBD Patients

1. Seek dietary counseling from an experienced dietitian
2. Avoid milk and milk products during active disease
3. Consume 10-20% more kcalories and 50% more protein with active disease
4. Do not avoid fiber, in fact try to increase fiber in diet as long as there is no obstruction in the GI tract
5. Follow a low residue diet if there is partial obstruction in the GI tract, consult with a physician and dietitian before making dietary changes
6. Prefer fish over other dishes (fish with high fat/fish oils such as catfish, salmon, etc., should be selected)
7. Take a multivitamin supplying 100% of RDA of vitamins and minerals, make sure to have monthly vitamin B_{12} injections if having CD
8. During inactive disease, consume foods that are rich in naturally occurring probiotics (such as yogurt containing lactobacillus)

Extraintestinal Manifestations

Unconfirmed reports suggest associations between resolution of pyoderma gangrenosum and uveitis with diet therapy.[133]

Ileal Resection and Kidney Stones

Patients with CD are at increased risk of oxalate kidney stones if their colons are relatively intact and they have had extensive ileal resections. Such patients should be advised to follow a low oxalate diet. Patients with a history of oxalate stones should also be treated with binding resins such as cholestyramine.

Nutritional tips for IBD patients are given in Table 57.12.

Short Bowel Syndrome

Definition and Epidemiology

Short bowel syndrome (SBS) is a malabsorptive state with a distinct group of symptoms and signs that occur as a consequence of major reductions in small intestinal absorptive surface area typically due to intestinal resection(s). Patients usually experience large-volume diarrhea with salient fluid and electrolyte losses as well as weight loss. The most important determinant of SBS is the length of the remaining functional small intestine, and less than 200 cm (6.5 feet) of length invariably is associated with compromised nutritional status. Less than 100 cm (3 to 3.5 feet) usually requires TPN. Small intestinal length is variable from person to person, with a range of 330 to 850 cm; therefore, the length of resected segments is clinically irrelevant. If there is doubt as to the length of the remaining small intestine, this crucial information can be obtained by doing a small bowel followthrough, since surgical and radiographic measurements correlate well.[134]

Although the true incidence and prevalence of SBS is not known, it is estimated that 10 to 20 thousand people in the U.S. require TPN as a result of it. The commonest causes of SBS are Crohn's disease, malignancy, radiation enteritis, and ischemic bowel. Others include jejunoileal bypass operations (used in the past to treat obesity), congenital abnormalities such as intestinal atresia, malrotation of the intestines, aganglionosis, and necrotizing enterocolitis in childhood.

TABLE 57.13

Factors That Affect the Type of Nutrition Required by SBS Patients

Factors	The Effect
Phases of SBS	See Table 57.14
Length of remaining small intestine	Very short lengths (60-100 cm) worsen severity of SBS
The extent of disease in remaining intestine	Impact of even mild disease on nutritional status can be profound. As disease worsens, the length of functioning small intestine decreases
Absence of the stomach	Loss of timed and slow release of gastric chyme decreases contact time between food and digestive/absorptive epithelium, thereby worsening SBS. Lack of stomach acid facilitates bacterial overgrowth aggravating malabsorption
Absence of the ileocecal valve	Leads to bacterial overgrowth enabling passage of colonic bacteria into the small intestine
Absence of the colon	Promotes water and electrolyte losses. Kcaloric losses are more extensive. Lack of gastrocolic reflex results in rapid transit of food, enhancing malabsorption

TABLE 57.14

Phases of SBS with Their Characteristics

Phase	Duration	Main Problems
Postoperative	1-2 weeks	High volume/severe diarrhea Gastric hypersecretion Related fluid and electrolyte imbalances
Transition	1-3 months	Diarrhea with oral intake Malabsorption: Increased kcaloric requirements Micronutrient deficiencies Social problems TPN related problems
Adaptation	3 months to 1-2 years	Dietary restrictions Adequacy of oral intake Complications: Renal stones Gallstones D-Lactic acidosis

Pathophysiology and Types of SBS

The main factors that affect the type of nutrition required by patients are listed in Table 57.13. The phase of SBS (i.e., the elapsed time after intestinal insult or surgery resulting in SBS) is of utmost importance in the acute management of SBS (Table 57.14). The remaining factors determine how well a patient will handle enteral nutrition in the long run.

In general, jejunal resections are better tolerated than ileal ones for several reasons:

1. Most of the intestinal fluid secretion that balances the osmotic load of gastric chyme entering the small bowel occurs in the jejunum. Subsequently, a large percentage of the proximally secreted water/electrolytes are absorbed distally in the ileum. Therefore, ileal as opposed to jejunal resections/insults result in more voluminous diarrhea, with loss of nutrients in stool.
2. GI transit is faster in patients with ileal resections because of the lack of the ileal brake mechanism, discussed in the first GI section.
3. The ileum has a greater adaptive potential.

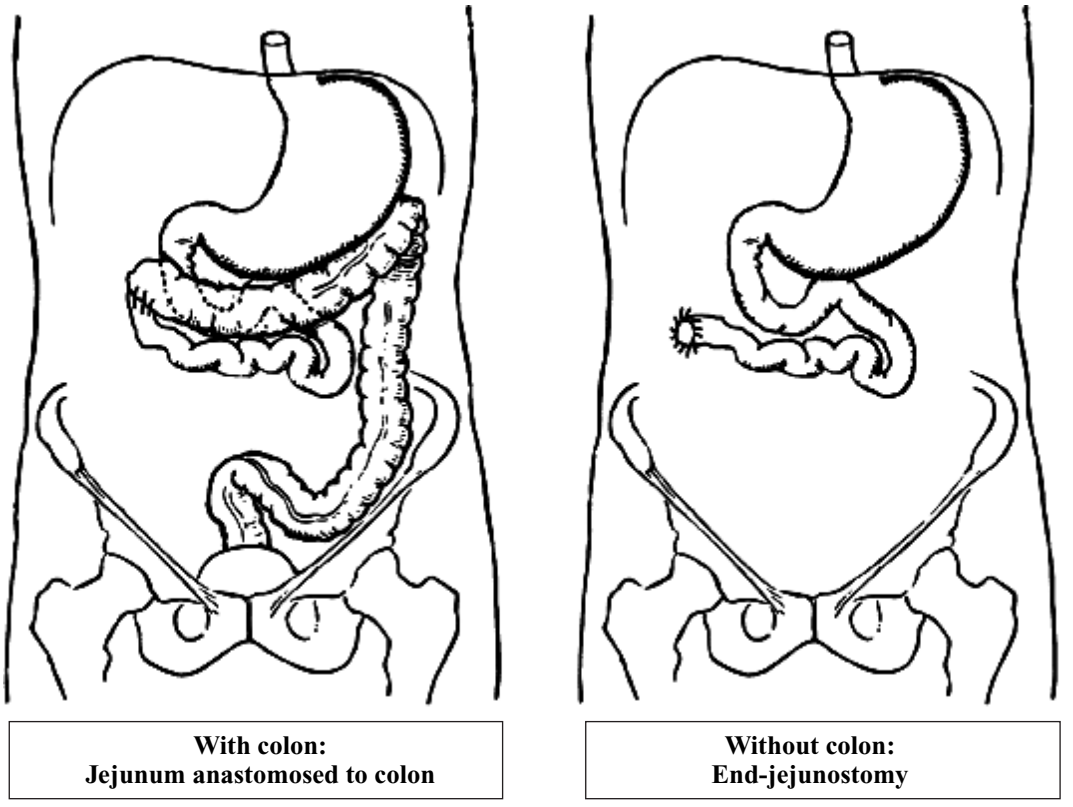

FIGURE 57.2
Anatomic types of short bowel syndrome.

Most patients with SBS fall into two main categories: those with and those without a colon. Patients with a colon usually have the majority of their ileum and some of their jejunum resected, with a resultant jejunocolic anastomosis. Those without a colon usually have end-jejunostomies (see Figure 57.2). Patients with a colon typically do better, especially in maintaining fluid and electrolyte balance, and cases with >50 cm of jejunum remaining may be managed with oral/enteral nutrition instead of TPN.

Diet in SBS

Dietary interventions in SBS should be individualized for each patient, as the needs differ considerably. Some general recommendations are given in the following paragraphs.

Postoperative Phase

No enteral nutrition is given at this phase because of the osmotic effects of food, and all patients require TPN. There are massive losses of fluids and electrolytes, and the amount is highly variable; therefore, careful monitoring of all intake and output as well as daily laboratory tests must be done. Patients should be given back their entire deficit plus an extra estimated 300 to 500 cc/day for insensible losses. Preferably, this type of replacement should be done on an hourly basis and separate from the TPN.

Agents that slow intestinal transit such as parenteral codeine and drugs that reduce the commonly seen gastric hypersecretion are also helpful in reducing the volume of stool

output. Gastric hypersecretion is usually comparable to the level seen in duodenal ulcer patients,[135] can lead to significant volume losses, especially within the first six months following surgery,[136] and can contribute to malabsorption by inactivating pancreatic lipase and deconjugating bile salts. Treatment with cimetidine has been shown to improve absorption.[136,137] A study of 13 patients with large-volume ostomy output has shown that omeprazole can increase water absorption in cases with fecal outputs >2.5 kg/day, but does not alter absorption of kcalories, macronutrients, or electrolytes.[138]

Octreotide (50 to 100 μg subcutaneously twice a day) has also been shown useful in patients with end jejunostomies who have >3 L/day of ostomy output.[139] Initial concerns that octreotide may delay adaptation have not been substantiated in animal studies.[140]

Transition Phase and Adaptation Phase

Oral Diet

In the transition phase, TPN is continued while patients are first started on isotonic clear liquids that contain salt and glucose. It is advised to wait until the ostomy output is less than 2 to 3 L/day before commencement of oral intake. The average sodium concentration in the ostomy secretions generally varies between 80 to 100 mEq/L, so the initial hydration solutions should have at least this amount. Alternatively, sodium in the ostomy secretions can be measured to calculate the concentration in the replacement solution. Patients who can tolerate these solutions should also be switched to oral antidiarrheals such as Loperamide, Lomotil, or tincture of opium. The commonly used dosages given in Table 57.15 are typically high.

Subsequently, patients should be transitioned into an oral diet. In general, patients with SBS do not tolerate large amounts of food at one time, foods with concentrated carbohydrates (especially mono and disaccharides) and high lactose, or foods high in oxalate and insoluble fiber. Hypotonic fluids such as water, tea, juices, and alcohol also need to be avoided, especially in patients without a colon, because this type of fluid draws sodium into the jejunal lumen, causing increased salt and water losses. Additionally, patients should be advised not to consume foods or supplements with non-absorbable sugars (such as sorbitol and mannitol) or non-absorbable fat (such as olestra), and to watch out for hidden diarrheal agents (e.g., polyethylene glycol found in certain mints). It is best to try small and frequent amounts of solid food until the patient can consume at least 1200 kcal/day without a significant increase in diarrhea. Once this is achieved, TPN may be gradually cycled to go on only during the night and then on alternate days, together with slow advancement of oral intake.

Enteral Feeding

Patients who are not able to take in adequate kcalories via the oral route should be tried on enteral feedings. There is no consensus on which type of enteral feeding is best for SBS, but isotonic polymeric formulas are recommended over elemental ones, which are expensive and poorly tolerated by patients because of their taste, smell, and high osmolality that increases jejunal secretion.

TABLE 57.15

Dosages for Antidiarrheals in SBS

Antidiarrheal	Typical Dosage
Loperamide	4-6 mg/4-5 times a day
Lomotil	2.5-5 mg/4 times a day
Tincture of opium	5-10 cc every 4 hours
Codeine phosphate	30 mg/3-4 times a day

TABLE 57.16

Selected Complications of TPN in SBS and Their Prevention/Treatment

Complication	Treatment
Line infections	Remove catheter completely if fungal infections or Staph. aureus are the cause (change over a wire is not acceptable) Staph. aureus requires 2-6 weeks of antibiotics Staph. epidermidis may be cured 80% of the time with 7-10 days of iv vancomycin
Bacterial overgrowth	Treat with broad spectrum antibitotics (tetracycline, ciprofloxacin, metronidazole, etc.) Rotate antibiotics every 4-8 weeks
Liver disease	Pursue enteral feedings aggressively Take care to prevent line infections Avoid overfeeding with excessive kcalories Prefer lipid kcalories to high carbohydrate nutrition Treat bacterial overgrowth Screen for cholelithiasis

Parenteral Nutrition

Patients who cannot stop TPN need to be monitored for complications such as feeding catheter infections, liver disease, bacterial overgrowth, and nutritional deficiencies. Some of these, together with their treatments, are given in Table 57.16.

Dietary Requirements and the Composition of the Diet in SBS

Energy

Most patients with SBS only absorb 50 to 60% of total energy, with the highest % malabsorption in fat and carbohydrates.[141] Thus, they need 1.5 to 2 times the amount of food/energy to maintain weight. For patients not able to increase their intake to this level, enteral feedings at night or additional TPN is required.

Carbohydrate versus Fat

In normal individuals, about 20% of all carbohydrates consumed exit the small bowel undigested and are fermented to SCFAs in the colon, where they are absorbed.[142,143] In order to take advantage of this colonic absorption, a well-designed study has compared the use of a high carbohydrate (60:20:20% of kcalories from carbohydrate: fat: protein) versus a high fat diet (20:60:20%) in SBS.[144] Intakes of the various diets did not affect stool or ostomy outputs, but consumption of the high carbohydrate diet by patients with a colon reduced the fecal loss of kcalories by 2 ± 0.2 MJ/day, which may equal up to 20 to 25% of the daily kcaloric intake of an average patient with SBS. Thus, patients with a colon should be advised to consume a high carbohydrate (50 to 60% of kcalories) and lower fat (20 to 30% of kcalories) diet. Diets containing more than 60% of energy as carbohydrates may ultimately overcome the colon's energy salvage capability of 2.2 MJ/day of SCFAs.[145]

In patients without a colon, neither high-fat nor high-carbohydrate diet significantly affects energy or water/electrolyte losses.[144] Furthermore, many patients with very short jejunal segments and high ostomy outputs have been shown not to need or benefit from any particular diet.[146,147] So, restriction of fat in the diet is not recommended, because such restriction limits palatability of food and deprives patients of valuable concentrated energy.

Long-Chain Fatty Acids (LCFAs) versus MCTs

There is a tendency to use MCTs because of their better absorption in the presence of a reduced bile acid pool and/or pancreatic insufficiency. MCTs can help reduce ostomy

output[148] in some cases, but they also exert a higher osmotic load in the small intestine and have a lower caloric density compared to LCFAs. Besides, LCFAs are better in inducing intestinal adaptation;[149] thus, a mixture of LCFAs and MCTs seems to be the most logical approach. A recent study compared the effects of a high fat (56% of kcalories as fat) diet in SBS. Patients were given fat in the form of LCFAs or a mixture of MCTs and LCFAs (about 1:1). Only patients with a colon benefited, with an increase in energy absorption from 46 to 58%.[150]

Lactose

Although the concentration of lactase in the intestine of SBS patients is unaltered, there is a reduction in the total quantity of available lactase. Thus, intake of food with high lactose content (e.g., milk) is discouraged, although many patients are able to tolerate small quantities of cheese and yogurt well.

Insoluble Fiber

Insoluble fiber such as bran decreases intestinal transit time and should be avoided by SBS patients.

Micronutrients

Deficiency of divalent cations such as calcium, magnesium, and zinc are typical. Water-soluble vitamin deficiencies are rare because most are absorbed in the proximal jejunum. Vitamin B_{12}, which is absorbed in the terminal ileum, and fat-soluble vitamins A, D, E, and K need to be replaced routinely. A water-soluble form of vitamin A (Aquasol A) may be tried. Monthly injections of 1000 μg vitamin B_{12} are necessary.

Bile Acid Replacement

Although the bile acid pool is reduced in patients with SBS, clinicians do not replace it routinely because of a fear that diarrhea will increase when bile acids are fermented by bacteria, causing secretion of water and electrolytes. A recent case report contradicts this and has demonstrated a 40 g/day increase in fat absorption when the patient was given a natural conjugated bile acid mixture isolated from ox bile or a synthetic bile acid named cholylsarcosine.[151]

Common Problems and Complications in SBS

Hypomagnesemia

Patients with end-jejunostomies tend to have hypomagnesemia more often than those with colons.[152] The condition requires parenteral magnesium frequently but oral 1-α-hydroxycholecalciferol may also be tried.[152] Urinary magnesium levels are a better indicator of deficiency than serum levels, which represent only 4% of the total body pool.[153]

Renal Stones

Risk of oxalate stones is increased, occurring in 25% of all SBS patients with a colon.[154] Calcium, which normally binds to oxalate and causes its excretion with feces, actually binds the malabsorbed fatty acids in the lumen in SBS, leaving oxalate available for absorption in the colon. Unabsorbed bile acids that enter the colon also stimulate absorption of oxalate.

Urinary oxalate excretion should be measured in patients with a colon, and oxalate should be restricted in patients with high levels of excretion. In patients with a history of

stones, restriction of fat in the diet may be considered. Additionally, urinary citrate and magnesium, which inhibit stone formation, are low and may need to be supplemented.

Gallstones

There is a two- to threefold increased risk of cholesterol gallstones because of the decreased bile acid pool in SBS. This increased risk is not different for patients with or without a colon, but risk of calcium bilirubinate stones is higher in patients on TPN because of gallbladder stasis and low oral intake. Cholecystokinin injections have been tried in dogs[155] with good success in preventing gallbladder stasis. Some advocate prophylactic cholecystectomy in SBS.[156]

Social Problems

Patients with end-jejunostomies and those dependent on TPN frequently have social problems that require help of psychiatrists and psychologists.

D-Lactic Acidosis

Fermentation of malabsorbed carbohydrates in the colon produces D-lactic acid that cannot be metabolized by humans. Elevated levels cause an anion-gap metabolic acidosis with confusion, ataxia, nystagmus, opthalmoplegia, and dysarthria.[157] The condition is more likely when thiamine deficiency is present, and it is treated with nonabsorbable antibiotics (neomycin or vancomycin) and restriction of carbohydrates (especially mono- and oligosaccharides) in the diet.[158]

In summary, nutritional management of SBS is complex, and patients should best be referred to an experienced multidisciplinary nutrition management team.

Acute Infectious Diarrhea

Acute infectious diarrhea usually does not affect nutritional status, even though it can result in severe water and electrolyte disturbances. Although no specific diet therapy is proven to be effective in this disease, patients should be encouraged to drink plenty of fluids that contain a mixture of glucose and sodium. Absorption of sodium in the intestinal tract is altered in acute diarrhea, but glucose-coupled sodium transport through the SGLT1 transporter is adequate in most cases to sustain hydration. An ideal mixture of glucose and sodium is found in the WHO oral rehydration solution (ORS), which can be made by mixing 20 g glucose, 3.5 g sodium chloride, 2.9 g sodium bicarbonate and 1.5 g potassium chloride in 1 L water. The commonly advocated sports drinks contain far less sodium and much more glucose compared to this ORS solution, and should not replace the latter. Within the last two decades, rice and other cereal-based ORS solutions that take advantage of other apical membrane sodium-dependent solute-transport transporters have been discovered. In these solutions, rice or cereal flour replace glucose found in the original ORS. The rice ORS solution is superior to the glucose-based ORS in decreasing stool output.[159] Most recently, induction of sodium absorption from the colon by short-chain fatty acids was observed.[160] A clinical application of this principle has been tested: 50 g/L amylase-resistant maize starch, which is malabsorbed and fermented to short-chain fatty acids by colonic flora, was added to the original WHO ORS. In adolescents and adults with *Vibrio Cholerae*-induced diarrhea, stool output and duration of diarrhea was

less in patients given the maize starch ORS compared to controls given standard ORS.[161] Further studies are needed before the latter is incorporated into common clinical practice.

Although it is rational to advise patients to stay away from hard-to-digest foods such as red meat, high fiber-containing vegetables (e.g., salads, greens, broccoli, etc.), and lactose, because of the increased rate of intestinal transit and concurrent malabsorption that occur in acute diarrhea, there exists no data in this regard. Most recently, an antidiarrheal factor has been found in rice, suggesting that a rice-based diet may be useful.[162] This factor blocks the secretory response of intestinal crypt cells to cyclic adenosine monophosphate and targets the cystic fibrosis transmembrane regulator (CFTR) chloride channel.

Clostridium Difficile Colitis and Probiotics

C. difficile colitis is a major cause of antibiotic-associated diarrhea and acute diarrhea in hospitalized patients. Spores of the bacterium are hard to destroy, and a mean of 20% (range 5 to 66%) of patients have recurrences despite treatment with effective antibiotics. Preliminary results of a trial with yogurt enriched in *Lactobacillus GG* (trial using medicinal microbiotic yogurt = TUMMY) together with standard antibiotic therapy have been promising in prevention of recurrence.[163] Final results are awaited for further recommendations.

Functional Disorders of the Gastrointestinal Tract (FGIDs)

Definition and Epidemiology

Functional gastrointestinal disorders (FGIDs) are the most common diseases of the GI tract, with at least 4.7 million affected individuals in the U.S. They comprise about 20 to 50% of gastroenterology clinic visits and are estimated to cost 8 billion dollars/year to the healthcare system. Definitions for the different types of FGIDs are established, and are known as the Rome II criteria.[164]

Mechanisms

Various factors and mechanisms thought to be important in the pathogenesis of these disorders are listed in Table 57.17. Currently recommended dietary management is based on decreasing food allergies, affecting GI motility and lowering intestinal gas production in an effort to decrease bowel wall distention.

Effects on Nutritional Status

FGIDs usually do not lead to weight loss. If a patient with FGIDs has significant weight loss, other causes should be sought. Although there are no reports of malnutrition, patients with FGIDs have many self-reported food intolerances, resulting in avoidance of various foods. This avoidance may lead to nutritional deficiencies. In one study comparing nutrient intake using 48-hour dietary recall, women with FGID had lower mean consumption of kcalories as well as folate, ascorbic acid, and vitamin A, compared to GERD and IBD patients.[165]

TABLE 57.17

Factors Important in Pathogenesis of FGIDs

1. Cognitive factors
a. Illness behavior
b. Illness coping strategies
2. Behavioral/Emotional factors
a. Psychosocial stress
b. Physical and/or sexual abuse
c. Anxiety
d. Depression
3. Physiological factors
a. Visceral hyperalgesia
b. Altered intestinal motility
c. Altered neuroendocrine response
4. Environmental factors
a. Dietary allergens
b. Enteric infections

Diet in FGIDs

There is no particular diet for patients with FGIDs, and there is little evidence for dietary therapies of functional upper digestive tract diseases. Some patients with functional chest pain may improve with diets similar to ones recommended for GERD patients (given in the previous GI section, Table 56.10). Others with functional dyspepsia may benefit from elimination of foods that delay gastric emptying (given in the previous GI section, Table 56.17).

Fiber for Irritable Bowel Syndrome (IBS)

Types of Dietary Fiber

Dietary fiber is defined as endogenous components of plants that are resistant to digestion by human enzymes. Fiber consists either of non-starch polysaccharides (e.g., cellulose, hemicellulose, pectins, and gums) or of non-polysaccharides (e.g., lignins composed of phenylpropane units). Cellulose is a non-digestible glucose polymer found in the cell walls of all vegetation, making it the most abundant organic compound in the world. Hemicellulose fibers are cellulose molecules substituted with other sugars, such as xylan, galactan, mannan, etc. Pectins and gums are composed of arabinose or galactose side chains added on to a galacturonate backbone; they naturally form gels.

Cellulose and hemicellulose are the major components of bran and whole grains. Lignins are commonly found in seeds and stems of vegetation. Pectin is part of apples, citrus fruits, and strawberries, and is widely added to jams and jellies. Gums naturally occur in oats, legumes, guar, and barley. Structural fibers such as celluloses, lignins, and some hemicelluloses are water-insoluble. Gums, pectins, psyllium, oat bran, and beans are water-soluble.

Insoluble fiber mainly adds bulk to stool and increases transit through the colon. Soluble fibers such as guar and pectin delay gastric emptying and transit through the small intestine, but speed transit through the colon and lower intraluminal pressures. Soluble fibers may also bind bile acids and minerals such as calcium and iron.

Bran

Fiber, in the form of bran, for IBS was popularized after Burkitt's initial work in early 1970s demonstrating that it increases stool weight and decreases intestinal transit time.

Others confirmed these findings,[166] and a lack of fiber was implicated for the development of many GI diseases including diverticular disease, colon cancer, and IBS. Consequently, studies in the 1970s undertook bran replacement as therapy for IBS, and the results were positive in some[167] but clearly negative in many others.[168] Most of these studies had methodological flaws, and were usually done with small numbers of patients. Nevertheless, given the lack of other effective therapies for the disease, bran became the standard of care.

Evidence over the last two decades contradicts this, and indicates that patients with IBS consume equal amounts of total fiber but less vegetable fiber compared to healthy controls.[169] Fiber replacement in the form of bran is no more effective than placebo,[170-172] and is poorly tolerated in many subjects. In one study, 55% of patients worsened after bran therapy, with deterioration in bowel habits, abdominal distention, and pain.[173] Improvement was seen in only 10%. These findings are corroborated by data from other studies upon careful review;[174] not only may patients worsen initially and not tolerate bran, but they also may have a high subsequent withdrawal rate.[175]

Soluble Fiber

Soluble fiber replacement seems to be better tolerated and more effective for IBS in comparison with bran.[176] It has also been used in combination with antispasmodics, anxiolytics, and antidepressants, and has a synergistic effect in such combinations[177] in some studies. Soluble fiber (such as psyllium, methylcellulose, or calcium polycarbophil) is most effective for constipation predominant IBS patients, and should be gradually increased over a period of weeks to avoid bloating and flatulence.

High-Fiber Diets

The role of a high-fiber diet for IBS is debatable, given the above controversies regarding bran as treatment for IBS. In an open-label trial, the symptoms that have been shown to benefit most from a high fiber diet are hard stools, constipation, and urgency. In this study, all patients who were able to consume 30 g or more fiber improved symptomatically.[178] In another trial of 14 patients followed for two to three years, 50% improved greatly, whereas 28.5% had worsening of their symptoms.[179] In conclusion, fiber is not ideal therapy for all patients with IBS, but should be tried especially in patients with constipation-predominant symptoms.

Food Allergies and IBS

Patients with IBS have many food intolerances, although a small number of these represent true food allergies. Food intolerances are typically to more than one item and are not specific, suggesting intolerance to food in general exists, rather than true food sensitivity. Problem foods are identified in 6 to 58% of cases, depending on the study.[180] The most common adverse food reactions, confirmed on double-blind challenge, are to milk, wheat, eggs, dairy products, corn, peas, tea, coffee, potatoes, nuts, wine, citrus fruits, tomatoes, chocolate, bananas, tuna fish, celery, and yeast. Some authors believe that these foods represent foods with a high salicylate content.[180] Many adverse reactions to food are not the classical wheal and flare type, a mere 3% are truly anaphylactoid-like and cause rash or swelling of the lips or throat,[181] and only some of the reactions are able to be confirmed by skin prick testing.[182] Most of the true food allergies in IBS are seen in patients with other atopic diseases.[183,184] Furthermore, most true food allergies on testing may not be clinically relevant. In a study of IBS patients, food intolerance was identified in 62.5%; skin prick tests to various foods were positive in 52.3%; but, strikingly, only

13.7% of the patients were symptomatic with foods that they were allergic to on prick tests.[182] These findings argue against undertaking a search for food allergies as part of the clinical evaluation of IBS patients.

A positive response to elimination diets in IBS ranges from 15 to 71%, but most studies have methodological flaws.[180] Supporting the role of food allergy in IBS, equal improvement of symptoms up to 50% has been noted in both study groups in trials with diet versus sodium chromoglycate administration for diarrhea-predominant disease.[185,186] These findings need to be confirmed in well-designed placebo controlled experiments before they can be considered clinically applicable, given a high placebo response rate in IBS.

Recently an *in vivo* colonoscopic allergen provocation (COLAP) test based on wheal and flare reactions in the colonic mucosa has been developed, and has shown positive reactions in 77% of patients with food-related symptoms.[187] The clinical utility of this test in IBS is yet to be determined.

In conclusion, a small subgroup of patients with true food allergies is classified as IBS. These patients tend to have atopy in general, and diarrhea-predominant disease. In selected patients, a symptom and food diary may be useful as an initial investigation for food allergy. Foods that lead to symptoms may then be eliminated and rechallenges may be done. Referral to an allergy specialist may be useful in such cases.

For the majority of cases, however, elimination of certain foods that the individual patient believes to cause symptoms is adequate therapy. Physicians also need to ensure that the patient's self-imposed dietary restrictions do not lead to macro- or micronutrient deficiencies.

Carbohydrates in IBS

Fructose and Sorbitol

A number of studies show that IBS symptoms are exacerbated in patients after ingesting fructose and sorbitol mixtures. Fructose is a natural ingredient of fruits, as is sorbitol. The latter is also a common sweetener in dietetic foods. Ingestion of 10 g of sorbitol, equivalent of 4 to 5 sugar-free mints or two medium pears, can produce moderate to severe abdominal discomfort, bloating, and diarrhea in 27% of healthy volunteers.[188] Symptoms may last up to six hours.

A subset of IBS patients has true malabsorption of fructose and sorbitol as assessed by breath hydrogen production,[189,190] although the level of breath hydrogen produced does not necessarily correlate with the degree of symptoms.[191] Whether fructose and sorbitol malabsorption is more common or more severe among IBS patients compared to healthy controls is uncertain. In one large study, there was no higher incidence or higher level of malabsorption.[192] Among malabsorbers, symptoms cannot be explained by changes in jejunal sensitivity and motor function of the small bowel. At present, avoidance of sorbitol and high intakes of fructose may be considered in selected patients.

Lactose

Subjective lactose intolerance is also increased in IBS, and lactose malabsorption is common. Most lactose malabsorbers among IBS patients are malabsorbers of fructose and sorbitol as well. However, elimination of lactose from the diet does not impact on the disease course or reduce symptoms when assessed objectively in long-term followup.[193] In contrast with these findings, many patients subjectively feel that identification of their lactose malabsorptive state has helped them gain awareness of food-symptom relationships and alleviate their symptoms partially. Treatment with lactase[194] or acidophilus milk

have shown no benefit over unaltered milk in IBS patients with and without lactose malabsorption.

Therapies Directed against Gas Production and Enzyme Therapies

Gas in the upper GI tract is a result of swallowed air and the carbon dioxide generated by chemical reactions of acid and alkali substances, whereas in the colon, gas forms as a result of fermentation of nutrients by the bacterial flora. Bloating and gas are common complaints of patients with IBS, even though the total amount of gas in the intestinal tract is not increased.[195] Rather, IBS patients have a hypersensitivity to the presence of gas, resulting in discomfort and pain. Therefore, therapies directed against gas seem reasonable in symptomatic patients.

In order to reduce air in the upper digestive tract, patients may be instructed to eat smaller quantities, avoid eating on the run, not talk during eating, avoid carbonated beverages, chewing gum, smoking, and excessive fluid intake with meals. Additionally, simethicone may be tried despite its questionable efficacy, as it poses no harm to patients other than their pocketbooks.[196]

One small study suggests that pancreatic enzyme supplements (30,000 USP lipase-112,500 USP protease-99,600 USP amylase) may reduce symptomatic bloating, gas, and fullness without significant decreases in breath hydrogen or methane levels in healthy subjects in response to a high-fat meal.[197] It is unknown whether the marginal symptomatic benefit in this study can be translated into patients with functional dyspepsia or IBS.

Activated charcoal has been shown to be partially effective in reducing gas in the lower GI tract.[196,198] A preparation called "Beano," containing the enzyme beanase, has been reported to reduce flatulence and breath hydrogen produced after ingestion of mashed black beans, although no studies exist demonstrating its clinical utility in IBS.[199]

It is commonly recommended that IBS patients avoid known gas-producing foods such as cabbage, legumes, lentils, beans, and certain cruciferous vegetables such as cauliflower and broccoli, although such a diet has not been tested, either. Interestingly, King and colleagues[200] have devised an elimination diet that reduces abnormal colonic fermentation. This diet allows meat and fish except beef, replaces all dairy products with soy products, eliminates all grains except rice, and restricts yeast, citrus, caffeinated drinks, and tap water. A pilot study of diarrhea predominant patients on this elimination diet has demonstrated reduction in median symptom scores, compared to controls. Further studies are needed before such a restrictive diet can be recommended for IBS in general.

Nutritional tips for patients with FGIDs are summarized in Table 57.18.

Diverticular Disease of the Colon

Definition and Epidemiology

Diverticular disease of the colon is common in Western countries. The incidence increases with age, but the true incidence is difficult to determine, since most patients remain asymptomatic. Nonetheless it is rare before age 40, and can be found in up to two-thirds of patients over the age of 80.[201-203] In contrast to Western countries (U.S., Australia, and European countries) diverticula are less common in South America, and extraordinarily rare in Africa and rural Asia. Owing to worldwide geographical variability, diverticular disease of the colon has been termed a disease of Western civilization.

TABLE 57.18

Summary of Nutritional Tips for the IBS Patient

1. If constipation predominant IBS, try soluble fiber supplements
2. If diarrhea predominant disease and atopic patient, keep food diary and seek help from an allergy specialist
3. Avoid only those foods that cause symptoms every time they are consumed
4. Replace consumption of heavily processed foods, containing preservatives, additives, food coloring, etc., with a natural balanced diet
5. Seek help from a dietitian to ensure adequate macro- and micronutrient intake if having to avoid many food items
6. Avoid gas-producing vegetables (e.g., legumes, cruciferous vegetables, etc.)
7. Avoid carbonated and caffeinated beverages

The majority of diverticula are histologically pseudodiverticula, which are herniations of the mucosa and submucosa through the muscular layer of the colon as opposed to true diverticula, which involve all layers. The sigmoid colon is the most frequent location for diverticular disease in the U.S.

Mechanisms

Role of Diet in the Pathogenesis

Dietary fiber deficiency along with the theory of colonic segmentation has been the leading hypothesis for the etiology of diverticular disease of colon. According to the segmentation theory, contraction of the colon at the haustral folds causes the colon to act as a series of "little bladders" instead of a continuous single-chambered lumen.[202] Formation of these segments leads to delayed transport, increased water absorption, and more importantly, a rise in intraluminal pressure, resulting in mucosal herniation.[204]

The incidence of diverticula within a society increases following the adoption of a Western diet that is low in fiber.[205] This is supported by animal data as well as epidemiological studies.[205,206] Compared to patients on a diet high in fiber content, those who consume a low-fiber diet have a threefold increase in the incidence of diverticulosis.[207] Consumption of a low-fiber Westernized diet leads to a lower intake of crude cereal grains, increase in consumption of white flour, refined sugar, conserves, and meat. Lack of "adequate" dietary fiber decreases stool weight, prolongs transit time, and increases the colonic intraluminal pressure, all of which predispose to the diverticula formation in concert with segmentation.[202,208] Additionally, a high meat diet changes bacterial metabolism in the colon, and bacteria may produce a toxic metabolite favoring diverticulosis, which is hypothesized to be a spasmogen, or an agent that weakens the colonic wall.[209]

Diet and Diverticulosis

Diet in Prevention of Diverticulosis

Given the importance of fiber in the pathogenesis of diverticula, it is reasonable to recommend a high-fiber diet in the prevention of diverticular disease. Confirming the importance of high-fiber diet as a prophylactic measure, the Health Professionals Follow-up Study, which included over 50 thousand health professionals, showed an inverse relationship between the amount of dietary fiber intake and the risk of developing symptomatic diverticular disease. Those who consumed more that 32 g/day of fiber had the greatest benefit.[210]

Diet in Treatment of Symptomatic Disease

The beneficial effects of dietary fiber on symptomatic uncomplicated diverticular disease continue to be subject to debate. Two controlled trials that evaluated the impact of fiber supplementation in patients with uncomplicated diverticulosis showed conflicting results.[211,212] However, this disagreement does not preclude the potential benefits from a trial of high-fiber diet, which still seems a reasonable approach. The American Society of Colon and Rectal Surgeons practice guidelines recommend the resumption of a high fiber diet following the resolution of uncomplicated acute diverticulitis.[213] In cases of complicated diverticular disease, the patient should be placed on clear liquid diet or be kept NPO in order to achieve bowel rest, which remains the mainstay of therapy along with the antibiotics. There is neither evidence nor scientific basis for avoidance of nuts, popcorn, or seeds for prevention of symptomatic attacks, even though this recommendation seems to be common.

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