Lecture Notes

Infectious Disease Pharmacotherapeutics

Advanced Pharmacotherapeutics

Learning Outcomes

1. Review Pathophysiology
2. Clinical Pharmacology
3. mechanism of action
4. PK/PD
5. Medication/Interactions
6. ADR's -Adverse drug reactions
7. RBA (Risk Benefit Analysis)
8. Review footnotes

1) Antibiotics
2) Antimycobacterial
3) Antivirals
4) Nucleoside analogues
5) Antivirals for hepatitis C
6) Antivirals for influenza
7) Anthelmintics
8) Metronidazole, nitazoxanide, and tinidazole
9) Antivirals: Nucleoside Analogues

Objectives

- Identify factors influencing the choice of an antimicrobial agent
- Differentiate between the multiple classes of antimicrobial agents
- Identify the efficacy of antimicrobial agents for the treatment of common infections in the primary care setting

1) In the Beginning . . .
    a. Sir Alexander Fleming (1928)
        i. Penicillium mold "must secrete antibacterial substance"
        ii. Discovered Penicillin

2) Bactericidal vs Bacteriostatic
    a. Bactericidal
        i. Kills bacteria
    b. Bacteriostatic
        i. Inhibits growth or reproduction of bacteria

3) Factors
    a. Pathogen – bacterial species or isolate

b. Antibiotic – appropriate dose, concentration

c. Organism growth conditions – overall host health

4) Antimicrobial Therapy

a. Selecting the Correct Antimicrobial

b. WHAT IS/ARE:

i. the most likely pathogen(s) causing the infection?

ii. the spectrum of a given antimicrobial activity?

iii. the likelihood of a resistant pathogen?

iv. the danger if there is treatment failure?

5) Antibiotic Dosage

a. Determination

i. Absorption and distribution = dose, route, frequency of administration

b. Minimum Inhibitory Concentration (MIC)

i. Lowest concentration of antimicrobial that will stop growth of a microorganism.

ii. Will vary by organism and by antibiotic

iii. Termed as susceptible, intermediate or resistant.

c. Minimum Bactericidal Concentration (MBC)

i. Lowest concentration of antimicrobial that will prevent growth of 99.9% of an organism

d. Recommended Doses are:

i. Usually dosed at 2-4 times the MIC

ii. “Over kill” to allow for variations in absorption and distribution

6) Antimicrobial Resistance

a. Leading Risk Factors

i. Overuse of broad-spectrum antibiotics

1. URI

2. Agricultural ABX use

3. Food supply globalization

ii. Daycare attendance

iii. Exposure to young children

iv. Multiple medical comorbidities

v. Immunosuppression

vi. Hospitalizations

1. Nasal MRSA in high-risk patients decolonize with Bactroban

7) Examples of Drug-Resistant Bacteria

a. Extended-spectrum beta-lactamases against E. coli and Klebsiella, carbapenem-resistant Klebsiella

b. Fluoroquinolone-resistant gonococcus

c. MRSA

d. Vancomycin-intermediate S. aureus.

8) Ways to Improve Antibiotic Use

a. Formulary restrictions

b. Evidence-based prescribing

c. Dose optimization

d. Antibiotic stewardship

i. Limit ABX use unless absolutely necessary

e. De-escalation

f. Resources

i. Infectious Disease Society of America (IDSA)

1. 10 x '20 initiative

2. https://www.idsociety.org/10x20/

ii. Society for Healthcare Epidemiology of America (SHEA)

1. Policy Statement on antimicrobial stewardship

2. http://www.shea-online.org/priority-topics/antimicrobial-stewardship

g. ABX prevention

i. Practice ABX stewardship

ii. Prevent infectious spread

iii. Contact precautions and good hand hygiene, wear PPI when necessary

Drugs Used to Treat Viral and Protozoal Infections

a) Pharmacodynamics
   (1) Antiviral drugs must either block entry into the cells or be active inside host cells to be effective.
      1. Acyclovir: active against herpes simplex viruses 1 and 2 (HSV-1 and HSV-2); varicella-zoster virus (VZV); Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes virus 6
      2. Valacyclovir: converted to acyclovir after oral administration and is active against the same viruses
      3. Famciclovir: active against HSV-1 and HSV-2, VZV, EBV, and hepatitis B virus
      4. Ganciclovir: active against CMV
   (2) Adverse drug reactions (ADRs)
      1. Acyclovir/valacyclovir: few ADRs when given orally
      2. Valacyclovir: may cause thrombocytopenia purpura, hemolytic uremic syndrome in immunocompromised patients
      3. Famciclovir: headache
      4. Ganciclovir: granulocytopenia, anemia, and thrombocytopenia; may be carcinogenic

b) Antivirals: Nucleoside Analogues
   (1) Drug interactions
      1. Few
   (2) Clinical use and dosing
      1. Herpes simplex: genital herpes, both initial outbreak and suppression therapy
      2. Herpes zoster (shingles): start therapy within 3 days of outbreak
      3. Varicella (chickenpox): start within 24 hours of outbreak
      4. Gingivostomatitis in children
      5. Bell's palsy
   (3) Rational drug selection
      1. Choice based on cost and convenience
   (4) Monitoring
      1. Rash for resolution
      2. Temperature
      3. Blood urea nitrogen and creatinine in high-risk patients
   (5) Patient education
      1. Drug started at earliest sign of infection
      2. Good hydration
      3. Symptoms of renal failure, encephalopathic changes, blood dyscrasias

c) Antivirals for Hepatitis C
   (1) Joint guidelines for treatment by American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (ISDA)
      1. Treatment of HCV infection based on the genotype and stage of the disease
   (2) Pharmacodynamics: most of HCV antivirals formatted as a fixed-dose combination of two antivirals
   (3) Pharmacokinetics: administered orally and widely distributed
   (4) Contraindications
      (a) BBW Black Box warning >> HPV reactivation and to test before starting HCV treatment
   (5) ADRs:
      (a) headache, fatigue, and nausea are the most frequent ADRs for all

(6) Drug interactions:
  (a) co-administration of ledipasvir and sofosbuvir (Harvoni) and amiodarone may cause serious symptomatic bradycardia
    1. Multiple drug interactions
(7) Clinical use specifics
  (a) dependent on the genotype of the HCV virus
  (b) renal and hepatic function
(8) Monitoring criteria (MUS-minimal use criteria s)
  (a) bilirubin, liver enzymes, and serum creatinine levels
(9) Patient education: taking medication daily, ADRs, drug interactions

d) Antivirals for Influenza
(1) Pharmacodynamics
  (a) Oseltamivir (Tamiflu), peramivir (Rapivab), zanamivir (Relenza) are used to treat influenza A and B.
    1. Sensitivity varies by year.
    2. Resistance to amantadine and rimantadine is common, so these drugs are no longer recommended for influenza.
(2) Pharmacokinetics
    1. Oseltamivir is well absorbed after oral administration.
    2. Zanamivir is inhaled; 4% to 17% is absorbed.
    3. Peramivir is administered intravenously (IV).
(3) ADRs
    1. Zanamivir: bronchitis and shortness of breath
(4) Clinical use specifics
    1. Oseltamivir, zanamivir: approved for the prophylaxis and treatment of influenza type A and B
    2. Peramivir is approved for acute influenza in those 18 years of age and older.
    3. Annual Centers for Disease Control and Prevention (CDC) updates of prescribing recommendations
      a. See: www.cdc.gov/flu
(5) Monitoring
    1. Renal function in older and debilitated patients
    2. Older patients: evaluate for confusion, hallucinations, and cognitive impairment
(6) Patient education
    1. Taking full course of therapy
(7) ADRs
    1. Annual influenza vaccination

e) Anthelmintics
(1) Pharmacodynamics
    1. Intestinal nematodes =mebendazole, pyrantel, and thiabendazole.
    2. Tissue nematodes =mebendazole, thiabendazole, albendazole, or ivermectin.
    3. pinworms very common in US. = 50 million cases per year
(2) ADRs
    1. Common: Nausea, vomiting, diarrhea, transient abdominal pain
    2. Mebendazole: may cause transient neutropenia
    3. Ivermectin: may cause Mazzotti reaction

a. Mazzotti reaction is a LIFE-THREATENING allergic reaction that occurs within 7 days. Symptoms include itching, fever, swollen lymph nodes, arthritis pains, headaches and abdominal pain.

(3) Clinical use specifics
1. Pinworms: single dose of mebendazole, pyrantel pamoate, or albendazole
2. Whipworms: pyrantel pamoate, albendazole, mebendazole
3. Roundworms: mebendazole
4. Hookworms: pyrantel pamoate, albendazole, mebendazole
5. Threadworm: ivermectin or thiabendazole
6. Scabies: off-label ivermectin in immunocompromised patients

(4) Rational drug selection
1. Use CDC recommendations.

(5) Monitoring
1. Assess for the eradication of the helminth.
2. Roundworms, hookworms, ascariasis, trichuriasis, and whipworms: stool samples are obtained before and 1 to 3 weeks after treatment for proof of cure.

(6) Patient education
1. Albendazole and mebendazole should be taken with a high-fat meal.
2. Ivermectin is taken on an empty stomach.
3. Albendazole should not be taken if pregnant and backup contraception should be used for 1 month after taking.
4. Metronidazole, Nitazoxanide, and Tinidazole

(7) Pharmacodynamics
1. Metronidazole treats both parasitical and bacterial infections.
2. Active against Trichomonas vaginalis, Entamoeba histolytica, Helicobacter pylori, Clostridium difficile
3. Nitazoxanide is used to treat Giardia lamblia and Cryptosporidium infections.
4. Tinidazole is active against amebiasis, giardiasis, and trichomoniasis.

(8) Pharmacokinetics
1. Metronidazole is well absorbed when taken orally.

(9) ADRs
1. Mitronidazole: anorexia, nausea, abdominal pain, dizziness, headache, metallic taste

(10) Clinical use and dosing
1. Metronidazole and tinidazole are used against the protozoal infections by T. vaginalis, G. lamblia, and E. histolytica.
2. Metronidazole is used for anaerobic bacterial infections and bacterial vaginosis and is one of the drugs in H. pylori treatment.

(11) Rational drug selection
1. Metronidazole is on the $4 retail lists.
   a. Avoid metronidazole in the first trimester of pregnancy.

(12) Monitoring
1. Resolution of symptoms
2. Signs of leukopenia

(13) Patient education
1. Administration
2. Metallic taste with metronidazole
3. Avoiding alcohol if taking metronidazole or tinidazole because of disulfiram-like reaction

4. Concurrent treatment of partner if sexually transmitted infection is present

Antimicrobial Therapy: Infectious Disease Pharmacotherapeutics

Antimicrobial Classes

Beta Lactams a. Penicillin's b. Cephalosporins c. Monobactams d. Carbapenems e. Macrolides	Fluoroquinolones	Tetracyclines
	Anti-anerobic Agents	Sulfonamides
	Glycopeptides	Aminoglycosides

Beta lactams

(1) Penicillins
- (a) Classified based on their spectra of activity natural versus synthetic
  - ***(i) Natural Pen V and G***
  - ***(ii)*** Semisynthetic: ***Procaine Pen G and Benzathine Pen G***
- (b) Penicillinase-resistant semisynthetic penicillin
  - ***(i) Cloxacillin, dicloxacillin, methicillin (broad spectrum), nafcillin, oxacillin (anti-staph drugs)***
- (c) Aminopenicillins
  - ***(i) Amoxicillin and ampicillin (2nd gen)***
  - ***(ii) Augmentin or Unasyn***
  - (iii) Extended spectrum penicillins
    1. ***Piperacillin tazobactam***
    2. ***Piperacillin (4th gen)***
    3. ***Carbenicillin (3rd gen)***
    4. ***Ticarcillin (3rd gen)***
- (d) MOA: inhibition of bacterial cell growth by interference with cell wall synthesis of activity: binding to and activating the ***penicillin-binding proteins (PBPs) interferes with peptidoglycan synthesis***
  - (i) Exhibit time-dependent bactericidal activity and post antibiotic effect against most gram-positive organisms
- (e) PKPD: Most are administered parenterally and are widely distributed in the body and penetrate CSF
  - (i) Most are excreted by the kidneys with a half-life is 30 to 90 minutes
- (f) Clinical uses: infections of upper and lower respiratory tract, urinary tract, and central nervous system (CNS) and sexually transmitted diseases
- (g) Adverse events: low incidence; most common are hypersensitivity reactions but also include nephritis, hyperkalemia, neutropenia and seizures

2) Beta-Lactam/Beta-Lactamase Inhibitors
- a) Role: to prevent the breakdown of the beta-lactam by organisms that produce the enzyme enhancing antibacterial activity
- b) Pharmacokinetics: diffuse into most body tissues except brain and CSF
- c) half-life is approximately 1 hour; eliminated by glomerular filtration
- d) Mechanism of action: wall-active agents

e) Clinical uses: treating polymicrobial infections
f) Adverse effects: hypersensitivity and GI side effects

Cephalosporins

Clinical indications

i) Skin and soft tissue infections, Exacerbation of chronic bronchitis (S.pneumoniae), AOM – PCN failure/PCN allergy, UTI – 2nd line therapy, STIs – cervicitis, urethritis (N.gonorrheae), ****Sinusitis – no longer recommended
ii) PK/PD
    (1) Well absorbed
    (2) Penetrate will into most tissues
    (3) Protein bound
    (4) Excreted via kidneys
iii) Adverse Reactions
    (1) Allergic reactions
    (2) Rashes
    (3) N/V/D
        (i) Hemolytic reactions – rare

Monobactams

(b) Aztreonam
    (i) Gram – organisms (pseudomonas; P. aeruginosa, Serratia marcescens)
    (ii) MOA: Interferes with bacterial wall synthesis; binds to and inactivates penicillin binding proteins
    (iii) PK/PD
        1. Distributes well
        2. Half-life = 2 hours
        3. Excreted unchanged by glomerular filtration
    (iv) Clinical Indications
        1. Complicated and uncomplicated UTI and URI; Pneumonia, bronchitis
    (v) Adverse Events
        1. Local reactions

1st Generation: Cephalexin	Gram + (MSSA); highest risk of cross reaction in PCN allergy
2nd Generation: Cefotetan	Gram +, enhanced Gram – coverage (H. influenzae, M. catarrhalis)
3rd Generation: Cefdinir	More active against gram -; varying Gram + reliability
4th Generation: Cefepime (injectable)	Gram -/+
5th generation: Ceftaroline	Gram+ better than 1st generation Cover MRSA & VISA

        2. GI symptoms

Carbapenems

(c) Imipenem (Primaxin); doripenem (Doribax)
(d) Active against aerobic gram + organisms (staphylococci) and gram - organisms (Enterobacteriaceae)
(e) MOA: Bind to penicillin binding proteins = interfere with bacterial wall synthesis

(f) PD/PK
  (i) Linear pharmacokinetics
  (ii) Widely distributed
(g) Clinical Indications
  (i) Single use agents
  (ii) Skin and soft tissue infections, Bone and joint infections, Lower respiratory infections

(4) Macrolides
(a) All with the –mycin suffix
(b) Azithromycin; Clarithromycin; Erythromycin
(c) Gram + organisms (S pneumoniae); select Gram – organisms (H. influenzae, M catarrhalis, atypical pathogens – M. pneumoniae)
(d) MOA: Inhibits bacterial protein biosynthesis
  (i) Bacteriostatic or bactericidal?
(e) Clinical indications
  (i) Community-Acquired pneumonia, STI's, Mycobacterium, Peptic ulcer disease, Endocarditis prophylaxis, Exacerbations of chronic bronchitis
(f) Pharmacokinetics
  (i) Well absorbed – distributes well to body tissues
  (ii) Potent inhibitors of CYP 450 3A4
  (iii) Half-lives varies (2 – 60 hours)
(g) Adverse Reactions
  (i) Neurotoxicity
  (ii) Lowers seizure threshold
  (iii) N/V, abdominal pain, cramping, diarrhea
  (iv) Integ: urticaria, eczema, Stevens-Johnson syndrome
  (v) Hepatotoxicity – rare

Fluoroquinolones

(h) 2nd Generation
  (i) Ciprofloxacin (Cipro)
  (ii) Gram – (E. coli); less dependable against Gram + (S. pneumoniae, S. aureus)
(i) 3rd Generation ("Respiratory Fluoroquinolones")
  (i) Levofloxacin (Levaquin), Moxifloxacin (Avelox), Gemifloxacin (Factive)
  (ii) Selective Gram + (S. pneumoniae, including DRSP), Gram – (H, influenzae), atypical pathogens (M. pneumoniae, C. pneumoniae
(j) MOA: Interfere with bacterial enzymes required for the synthesis of bacterial DNA
  (i) Display a concentration-dependent killing effect
  (ii) Excellent bioavailability for transition from IV to oral form
  (iii) Distribute well into most tissues and fluids (except CNS)
  (iv) ½ Life ranges: 4 to 12 hours; elimination is renal
  (v) Strong inhibitors of deoxyribonucleic acid (DNA) gyrase and topoisomerase IV
  (vi) activity against aerobic gram-negative organisms
(k) Clinical Indications
  (i) Exacerbation of chronic bronchitis, Community-Acquired pneumonia, UTIs, STIs, Skin and soft tissue infections, Infectious diarrhea
(l) Adverse Reactions
  (i) GI: pseudomembranous colitis
  (ii) CNS: sleep disorders, dizziness, acidosis

(iii) Renal/hepatic failure
(iv) CV: angina, atrial flutter
(v) Black Box : Tendonitis/tendon ruptures
1. Elderly at higher risk
2. Onset may be delayed – 120 days to months
3. Do not prescribe to children <18
4. Avoid in pregnancy

Lincosamides: Clindamycin (Cleocin)

(m) Pharmacodynamics: inhibits protein synthesis
(i) No gram-negative activity
(ii) Gram-positive activity: Corynebacterium acnes, Gardnerella vaginalis, some MRSA
(n) Pharmacokinetics: oral dosing completely absorbed; not affected by gastric acid
(o) Clinical use and dosing
(i) First-line therapy for MRSA in some areas
(ii) Infections in PCN-allergic patients
(iii) Drug-resistant Streptococcus pneumoneae infections
(iv) Dental infections
(p) Rational drug selection
(i) Considered second-line therapy, narrow spectrum of aerobic activity
(ii) First-line therapy in special populations (pregnant women and children)
(q) Monitoring
(i) Stop medication if significant diarrhea occurs.
(r) Patient education
(i) Finishing therapy
(ii) ADRs: diarrhea
1. ADRs: Black Box warning for severe colitis; dermatological: rash, burning,) itching, erythema; transient eosinophilia, neutropenia, thrombocytopenia

Tetracyclines

h. "Cycline" suffix
i. Tetracycline, Doxycycline, Minocycline
j. Active against non-resistant strains of S. pneumoniae, M. catarrhalis, and atypical pathogens – M. pneumonia, C. pneumoniae
k. MOA: Bind to the 30S subunit of the bacterial ribosome, inhibiting bacterial protein synthesis
i. Bacteriostatic or bactericidal?
l. PK/PD
i. Lipid soluble
ii. Food decreases absorption
iii. Excellent tissue distribution
m. Clinical Indications
i. Genitourinary infections, Acne, Peptic ulcer disease, Lyme disease
n. Adverse Reactions
i. GI: anorexia, N/V/D, esophageal ulcers
ii. CNS: dizziness, lightheadedness
iii. Integ: photosensitivity, rashes, blue/grey pigmentation

Sulfonamides

1) Trimethoprim
   a) Sulfamethoxazole
   b) TMP-SMX (Bactrim, Septra)
   c) Sulfasalazine (Azulfidine)
2) Active against select Gram – organisms (E. coli), select Gram + organisms including MRSA
3) MOA: Folate synthesis inhibition competes with an enzyme (PABA) that is needed for folate synthesis. Folate needed for cellular division
   (1) Bacteriostatic or Bactericidal??
4) Pharmacokinetics
   (1) Readily absorbed and distributed widely
5) Clinical Indications
   (1) UTIs, URIs, Exacerbations of chronic bronchitis, MRSA
6) Adverse Reactions
   (1) GI: anorexia, N/V/D, stomatitis
   (2) Integ: rashes; hypersensitivity reactions; photosensitivity
   (3) CNS: H/A; dizziness
   (4) Avoid in G6PD deficiency; individuals with folate deficiency or blood dyscrasias

Glycopeptides

b) Vancomycin; dalbavancin; oritavancin
c) Gram positive aerobic and anaerobic bacteria (MRSA)
d) MOA: Cell wall agents – inhibit bacterial wall synthesis
e) PK/PD
   i) Poorly absorbed in GI tract
   ii) Dose adjust in renal impairment
f) Clinical Indications
   i) Serious gram-positive infections, Drug of choice for MRSA, Neutropenic fever, endocarditis, meningitis, C. Diff
g) Adverse Reactions
   i) Fever, chills, phlebitis
   ii) "Red Man Syndrome"
   iii) Nephrotoxicity, ototoxicity

Aminoglycosides

h) Gentamicin, tobramycin, streptomycin
i) Aerobic gram – bacilli (E-choli; Klebsiella)
j) MOA: Bind to bacterial ribosomes = inhibit bacterial protein synthesis
k) PK/PD
   (1) Poorly absorbed in the GI tract
   (2) Half-life = 1 to 3 hours
   (3) Dose adjust in renal impairment
   (4) Narrow therapeutic drugs
l) Clinical Indications
   i) Nosocomial infections, often use with other agents: Pneumonia, bacteremia, intra-abdominal and skin and soft tissue infections, TB
m) Adverse Reactions
   i) Nephrotoxicity, ototoxicity

ii) Anti-anaerobic Agents-metronidazole

n) Clinical Indications
   i) Mixed infections, BV, Trichomoniasis, C. difficile

o) Adverse Reactions
   i) N/V; abdominal pain
   ii) Metallic taste
   iii) Seizures, peripheral neuropathy, pancreatitis

Anti-anaerobic Agents

p) Metronidazole
q) Gram – and gram + anaerobes, H pylori, protozoa
r) MOA: interferes with bacteria DNA synthesis
s) PD/PK
   i) Penetrates into most tissues
   (1) Metabolized by liver
   (2) Half live 6 to 9 hours

SELECT PATHOPHYSIOLOGIAL DISEASES/SYNDROMES

1) Urinary tract infection (UTI) is a broad term used to describe inflammation of the urethra, bladder, and kidney.
   a. Bacteria, yeast, or chemical irritants can cause inflammation in the urinary tract. A positive urine culture (≥105 CFU/mL) with no more than two uropathogens and pyuria confirms the diagnosis of UTI.
   b. UTIs are a common problem encountered in health care. Each year It is estimated at least 150 million cases of symptomatic UTIs worldwide (Foxman, 2014).
   c. Cystitis/Urinary Tract Infection
      i. Definition
         1. Broad term used to describe inflammation of the urethra, bladder, and kidney
      ii. Causes
         1. Bacteria, yeast, or chemical irritants =inflammation of urinary tract
         2. Asymptomatic bacteriuria >> symptomatic >> recurrent UTIs, >> sepsis associated with UTI requiring hospitalization.
      iii. Factors influencing the development of an UTI
         1. Virulence of the organism
         2. The inoculum size
         3. The adequacy of the host's defense mechanisms
      iv. Clinicals Presentation
         1. Classic triad
            a. Urinary urgency, Urinary frequency, Dysuria
         2. Other symptoms
            a. Pressure/fullness in the suprapubic area; back pain

3. Pyelonephritis: flank pain, nausea and vomiting, and temperature greater than 100.4°F (38°C)

v. Risk factors
   1. Diabetes, functional disability, Recent sexual intercourse, Prior history of urogynecologic surgery, Urinary retention, Urinary incontinence

vi. Types of Urinary Tract Infections
   1. Uncomplicated UTI
      a. Occurring in a premenopausal, sexually active, nonpregnant woman who has not recently had a UTI
   2. Complicated UTI
      a. One that occurs in a man, a postmenopausal or pregnant woman, or a patient with urinary structural defects, neurologic lesions, or a catheter.
      b. A UTI also is considered complicated if symptoms have persisted for more than 7 days.

d. Goals of Therapy
   i. Destroy the offending organism
   ii. Relieve symptoms
   iii. Prevent complications

e. Rational Drug Selection
   i. Drug therapy
   ii. Spectrum of activity: need gram-negative coverage
   iii. Empirical treatment with nitrofurantoin
      1. Not recommended for use in febrile infants and children
   iv. Alternative or second-line therapy with cephalosporins (cefpodoxime, cefixime)

f. Recommended Order of Treatment for Uncomplicated Cystitis
   i. First line (Empiric SOC)
      1. Bactrim 3-day oral therapy (TMP-SMZ)
      2. Macrobid 7-day therapy (nitrofurantoin)
   ii. Second line (Empiric SOC)
      1. Bactrim 7-day oral therapy of TMP-SMZ
      2. Cipro 7-day oral therapy (ciprofloxacin, levofloxacin, ofloxacin, norfloxacin
   iii. Third line
      1. Culture and sensitivity testing—treat on results

g. Agents for Urinary Tract Infection: Antibiotics
   i. Trimethoprim–sulfamethoxazole (Bactrim)
      1. Children: 5 mg/kg/d in divided doses for 10 days
      2. adults: 1 DS ql2h for 10 days
   ii. Trimethoprim (Trimpex)
      1. 100 mg q12h for 3 days
   iii. Nitrofurantoin (Macrobid, Macrodantin)
      1. Macrobid—100 mg q12h for 7 days
      2. Macrodantin—100 mg qid for 7 days
      3. Fosfomycin (Monurol) 3-gm packet × 1

h. Resistance Patterns
   i. E. coli to trimethoprim-sulfamethoxazole (TMP/SMZ) ciprofloxacin and levofloxacin=15% to 20%.

ii. Do not use Amoxicillin in US. Approx. 1/3 UTI organisms are resistant.

i. Urinary Analgesics
   i. Methenamine (Urised): 2 tabs qid
      1. May cause blue-green discoloration of urine or feces; is not antibacterial
   ii. Phenazopyridine (Pyridium): 200 mg tid
      1. Discolors urine and clothes (red orange); is not antibacterial
   iii. Flavoxate (Urispas): 100–200 mg tid–qid
      1. Take after meals; reduce dose on improvement

j. SPEC POPS: Elderly
   i. Often asymptomatic; may cause LOC (level of consciousness) and are at increased risk for UTIs
   ii. Postmenopausal females are more prone because there are uropathogens-dominant vaginal flora with the loss of estrogen. Lactobacilli diminish and pH increases
   iii. For male patients most often seen with prostatic hyperplasia, partial obstruction, or persistent prostatitis.

k. SPEC POPS: Pregnancy
   i. Asymptomatic bacteriuria occurs in approximately 7% of pregnant women. Of these, pyelonephritis develops in 30% if the bacteriuria is not treated
   ii. Untreated UTIs can contribute to prematurity or stillbirth
   iii. Amoxicillin is effective in approximately two thirds of UTIs in pregnant women and is safe for the fetus. Also safe are cephalexin and nitrofurantoin (only during the first and second trimesters). Sulfonamides are safe except in the last trimester.

l. SPEC POPS: Children
   i. may indicate a genitourinary structural anomaly. Accurate diagnosis usually requires invasive collection of urine, especially in young children

m. First-line antimicrobial agents include:
   i. β-lactams amoxicillin–clavulanate (25–45 mg/kg/d divided every 12 hours)
   ii. cephalexin (25–50 mg/kg/d divided every 6–12 hours)
   iii. cefpodoxime (10 mg/kg/d divided every 12 hours)
   iv. TMP-SMX (8–10 mg/kg/d divided every 12 hours)

n. Monitoring
   i. Acute UTI in women
      1. Symptom resolution in 48 hours
   ii. If symptoms persist, urine culture performed
   iii. Patients with recurrent infections
      1. Culture urine.
   iv. Post-treatment urinalysis to rule out persistent infection
   v. Children under 5 years of age
      1. Urine culture
      2. Re-culture at end of therapy
      3. May need radiological workup
   vi. Pregnancy
      1. Need follow-up urine culture every 2 weeks until delivery

o. Outcome Evaluation
   i. Infants and children younger than 5 years of age
   ii. Consider anatomical problem, such as vesicoureteral reflux.
   iii. Adults require workup and possible referral to urologist for:

p. Gross hematuria

i. Symptoms of obstruction
ii. Persistent UTI
iii. Symptoms during pregnancy
iv. Fever or dehydration

q. Patient Education
    i. Medications
        1. Take medications as prescribed.
        2. Complete full course of antibiotics.
    ii. Lifestyle management
        1. Ingest cranberry juice or extract.
        2. Avoid spermicides and diaphragms.
        3. Women: Void after intercourse.
        4. Drink 2,000 mL/day of fluids.
        5. Do not resist ur ge to void.

STI's

1. **DEFINE:** Sexually transmitted infections (STIs) are among the most common illnesses in the world. They have far-reaching health, social, and economic consequences
2. **GUIDELINES** emphasize the development of management strategies that are adaptable to the managed care environment and are considered the gold standard for treating STIs
3. **GOT:** The goals of therapy for all STIs are to eradicate the causative organism and prevent complications
4. **METHOD:** the DDX of dysuria (discomfort, burning, or sensation of pain during micturition. Location is external (urine irritating the inflamed genital organs) or internal (pain felt in the urethra). Divided into 2 categories: infectious and non-infectious) includes s/sx of: urgency, frequency, back pain, abdominal pain, fever, hematuria, and costovertebral angle tenderness. Vaginal irritation or discharge makes the diagnosis less likely; however, these symptoms do not entirely rule out UTI as a diagnosis. focused physical exam, urinalysis genital exam and investigations should be guided by the initial detailed history

Gonorrhea (*Neisseria gonorrhoeae)*

a. DEFINE¿) is a gram-negative diplococcus bacteria that is closely related to other human Neisseria species and has affinity for human mucosal epithelium that is mediated by outer membrane proteins.
b. N.gonorrhoeae can elude the immune system by changing the outer membrane antigens through genomic plasticity related to DNA mutation or recombination with related species. Of special importance, chromosomal DNA changes and plasmid transfer have mediated resistance to many common antibiotics. Humans are the only known host
c. Classic presentation is a man with a urethral discharge; women are often asymptomatic, but may have vaginal discharge
d. Strains of Gonorrhea
    i. Certain strains of the organism are resistant to sulfonamides.
        1. Penicillinase-producing N¡.gonorrhoeae and chromosomal-resistant N¡. gonorrhoeae are resistant to penicillin.
        2. Tetracycline-resistant N¡.gonorrhoeae is resistant to tetracycline.
e. Antibiotic Therapy for Gonorrhea

i. ***First line:***
   1. Ceftriaxone 250 mg IM once PLUS azithromycin 1 g PO once
   2. or doxycycline 100 mg PO bid for 7 days

ii. ***Alternative***
   1. Cefixime 400 mg once
      a. Cephalosporins
         i. Divided into "generations" based on their antimicrobial spectrum of activity.
      b. Pharmacokinetics: well absorbed from the GI tract; penetrate into tissues and body fluids; high concentrations in urinary tract; most are excreted by the kidneys.
      c. MOA: interfere with bacterial cell wall synthesis by binding to and inactivating PBPs.
      d. Uses: used in treating many infections; favorable toxicity profile.
   2. Clinical dosing
      a. **cephalosporin, 3rd generation infections, gonococcal.** uncomplicated infection, initial or recurrent
      b. Dose: 250 mg IM x1; Info: for infections of pharynx, cervix, urethra, rectum
      c. use w/ azithromycin (preferred) or doxycycline regardless of chlamydia test result
   3. Interaction Characteristics: alters GI flora, bactericidal activity requires bacterial growth, impairs immunomodulatory bacterial infective agent
   4. ADR's
      a. **Common Reaction:** local injection site rxn, eosinophilia, thrombocytosis, ALT, AST elevated, diarrhea, leukopenia
      b. **Serious Reactions:** anaphylaxis, bronchospasm, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, serum sickness, pneumonitis, hypersensitivity, neutropenia, leukopenia, hemolytic anemia ++++ many more
   5. PK/PD/Monitoring
      a. **MOA**: bactericidal; inhibits cell wall mucopeptide synthesis
      b. **Monitoring criteria:** PT; if renal or hepatic impairment, cancer, malnutrition, long-term antimicrobial tx, or anticoagulant tx
      c. **Metabolism:** other; CYP450: unknown
      d. **Excretion:** Half-life: 5.8-8.7h, 15.7h (CrCl 5-15); urine (33-67% unchanged), bile/feces.

iii. What should I know before I write (cephalosporins-high yield information)
   1. an allergy to any drugs (especially penicillins)
   2. kidney disease (or if you are on dialysis) or liver disease
   3. diabetes
   4. gallbladder disease
   5. a stomach or intestinal disorder such as colitis
   6. poor nutrition
   7. a condition for which you take a blood thinner (warfarin, Coumadin, Jantoven)

Chlamydia

f. DEFINE:.Chlamydia.trachomatis, which is almost always transmitted by sexual contact, and it is the most commonly reported sexually transmitted infection in the US.
    i. In females, there may be cervical inflammation or yellow, cloudy discharge from the cervical os. In male, there may be a discharge from the penis.
g. Causative agent: Chlamydia.trachomatis transmitted sexually or perinatally
h. Symptoms: more than half of infected patients have no clinical signs or symptoms
    i. Women: vaginal discharge, mucopurulent cervicitis with edema and friability, urethral syndrome or urethritis, pelvic inflammatory disease (PID), ectopic pregnancy, infertility, and endometritis
    ii. Men: thin, clear discharge, and dysuria
i. Antibiotic Therapy for Chlamydia
    i. **First line**
        1. Azithromycin 1 g PO once or.Doxycycline 100 mg PO bid for 7 days
    ii. ***Alternative***
        1. Erythromycin base 500 mg PO qid for 7 days or
        2. Erythromycin ethylsuccinate 800 mg PO qid for 7 days or
        3. Ofloxacin 300 mg bid for 7 days or
        4. Levofloxacin 500 mg PO for 7 days
    iii. Macrolides and Ketolides
        1. Erythromycin (E-Mycin), the prototypical macrolide, has been used in treating many infections over the years. However, its use has been diminished by GI side effects.
        2. Pharmacokinetics: oral; absorbed from the GI tract; good tissue penetration, high intracellular concentration, minimal protein binding; metabolized via liver.
        3. Clinical uses: respiratory tract, skin, and soft tissue infections, sexually transmitted diseases, HIV-related Mycobacterium.avium–intracellulare complex infection, other infections caused by atypical organisms.
    iv. Tetracyclines
        1. Possess activity against gram-positive, gram-negative, and atypical organisms, including rickettsiae, chlamydia, mycobacteria, and spirochetes.
        2. They are separated into short-, intermediate-, and long-acting agents.
        3. Doxycycline and minocycline are considered long-acting and the most active of the class.
        4. Used in many settings and as alternatives when beta-lactams are not an option; frequently used to treat rickettsial, chlamydial, and gram-negative infections.
    v. Other Drugs Used to Treat Chlamydial Infections
        1. Doxycycline (Vibramycin); Adult: 100 mg bid for 7 days; Child (≥8 years): 100 mg PO bid for 7 days
        2. Amoxicillin (Augmentin): Pregnancy: 500 mg tid for 7 days
        3. Ofloxacin (Floxin): 300 mg bid for 7 days

5. Antibiotic Therapy for Pelvic Inflammatory Disease
    a. Ceftriaxone 250 mg IM once or Cefoxitin 2 g IM and probenecid 1 g PO once and doxycycline 100 mg PO bid for 14 days
    b. PLUS

c. Doxycycline 100 mg PO bid for 14 days
d. WITH OR WITHOUT
    i. Metronidazole 500 mg PO bid for 14 days

Drug monograph Azithromycin	**Information**
MOA (mechanism of action)	bacteriostatic or bactericidal, depending on susceptibility and concentration; binds to 50S ribosomal subunit, inhibiting protein synthesis
Medication interactions	1. Moderate P-gp inhibitor (metabolism) 2. affected by delayed gastric emptying and alters GI flora 3. impairs immunomodulatory bacterial infective agent 4. prolongs QT interval (known)
Dosing in STI's	Azithromycin (Zithromax): Adult: 1 g PO single dose; Pregnancy: 1 g PO in a single dose; Child (≥45 kg, <8 years): 1 g PO in a single dose; Child (≥8 years): 1 g PO in a single dose (or doxycycline as below)
PK/PD	1. Metabolism: liver; CYP450: unknown 2. Excretion: bile primarily (>50% unchanged), urine (6% unchanged) 3. Half-life: 68h; Info: extensive uptake and eventual release from tissues
Monitoring Criteria	no routine tests recommended
ADRs	Common Reactions Diarrhea/nausea/vomiting, abdominal pain, dyspepsia, dizziness, rash, flatulence, headache, anorexia, pruritus, impaired hearing (high dose use) Serious Reactions Angioedema, anaphylaxis, cholestatic jaundice, hepatotoxicity, pancreatitis, infantile hypertrophic pyloric stenosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rxn w/ eosinophilia and systemic sx, C. difficile-assoc. diarrhea, QT prolongation, torsade's de pointes, myasthenia gravis exacerbation
Additional med teaching points	Photosensitivity: Avoid exposure to sunlight or tanning beds r/t you may burn more easily. Wear protective clothing and use sunscreen (SPF 30 or higher) when you are outdoors.

Genital infections w/rash

e. What is it? STI with distinguishable rash and treatment modalities. Most common STI's with rashes are Herpes, syphilis, and HPV-genital warts

Genital herpes

i. DEFINE: Infection with HSV-1 or HSV-2 can cause oral, genital, and ocular ulcers.
ii. Most people have unrecognized disease, and it is acquired via mucosal surfaces or breaks in the skin. The virus initially replicates in the epidermis, then infects sensory or autonomic nerve endings and travels by retrograde axonal transport to sensory ganglia where it stays for life of individual.
iii. Symptoms of genital herpes range from asymptomatic to tingling and burning without lesions, to recurrent genital ulcerations
iv. Diagnostic Criteria for Genital Herpes
    1. A diagnostic evaluation for herpes includes a health history and physical examination.
    2. In addition to serologic testing for HSV, patients should have a serologic test for syphilis.
        a. HIV testing should be considered as well.
        b. Specific tests for genital herpes include culture or antigen test for HSV, and a POCkit-HSV-2 test.
v. Antiviral Therapy for Genital Herpes
    1. Mechanism of Action for antivirals
        a. inhibits DNA polymerase; incorporates into viral DNA
    2. Initial.episode.treatment for 7–10 days
        a. Acyclovir 400 mg PO tid or acyclovir 200 mg PO five times a day or valacyclovir 1 g PO bid
    3. Recurrent.treatment
        a. 400 mg PO tid for 5 days or acyclovir 800 mg bid for 5 days or. famciclovir 125 mg PO bid for 5 days or famciclovir 100 mg bid for 1 day or valacyclovir 500 mg PO bid for 3 days or valacyclovir 1 g once a day for 5 days
    4. Suppressive.treatment
        a. Acyclovir 400 mg bid or famciclovir 250 mg bid or valacyclovir 500 mg or 1,000 mg qd
    5. Interaction Characteristics: Weak CYP1A2 inhibitor, impairs immunomodulatory viral infective agent, lowers seizure threshold, nephrotoxicity
    6. Monitoring Parameters: Cr at baseline
    7. Metabolism: other; CYP450: unknown
    8. Excretion: urine; Half-life: 2.5-3.3h

Human Papillomavirus

f. DEFINE¿Human Papillomavirus (HPV) infection of abraded skin
g. Rash: Flesh colored exophytic lesions on genitalia with a variable appearance from a small, soft, fleshy flat-topped Papules or larger cauliflower-like or vegetating masses. Varies from tiny asymptomatic lesions to large Plaques. May interfere with sexual intercourse, urination and defecation. Lesion size is not correlated with cancer risk
h. Medications.used.

i. Patient.applied.
    1. Podofilox 0.5% solution or gel for 3 days, then 4 days of no therapy
    2. Imiquimod 5% cream three times a week up to 16 weeks
ii. Provider.applied
    1. Podophyllin resin 10%–25% in compound of tincture of benzoin weekly as needed
    2. Trichloroacetic acid or bichloracetic acid 80%–90% weekly as needed
iii. Podofilox
    1. Metabolism: unknown; CYP450: unknown; Info: minimal systemic absorption
    2. Excretion: unknown; Half-life: 1-4.5h
    3. Mechanism of Action: exact mechanism of action unknown; inhibits cell mitosis
    4. Parameters: no routine tests recommended

Syphilis

i. DEFINE: common sexually transmitted infection caused by spirochetal bacterium Treponema.pallidum, subspecies pallidum. Approximately 10 million to 12 million new infections worldwide each year. Diagnosis is usually straightforward after clinical exam and serologic tests. Treatment is with penicillin.
    i. Untreated syphilis facilitates HIV transmission and causes considerable morbidity, such as cardiovascular and neurologic disease.
    ii. Rash: Solitary Chancre (hallmark of Primary Syphilis) which is a painless papule ulcerated with Indurated lesion with smooth base and firm border. Multiple lesions may be present

j. Diagnostic Criteria for Syphilis
    i. Primary infection: ulcer or chancre at the infection site that erupts approximately 3 weeks after exposure
    ii. Secondary infection: low-grade fever, malaise, sore throat, hoarseness, headache, anorexia, rash, mucocutaneous lesions, alopecia, and adenopathy
    iii. Tertiary infection: cardiac, neurologic, ophthalmic, auditory, or gummatous lesions

k. Antibiotic Therapy for Syphilis
    i. Early.primary?secondary?or.latent.syphilis <7.year
        1. Adult: benzathine penicillin G 2.4 million U, IM single dose
        2. Child: 50,000 U/kg, IM, single dose up to 2.4 million U
    ii. Latent disease >7.year.or.unknown.duration
        1. Adult: benzathine penicillin G 2.4 million U, IM, for 3 doses at 1-wk intervals
        2. Child: 500,000 U/kg, IM, for 3 doses at 1-week intervals

l. Selected Drugs to Treat Neurosyphilis
    i. Aqueous crystalline penicillin G 18–24 million U/d, give as 3–4 million U IV q4h for 10–14 days
    ii. Procaine penicillin (Bicillin with probenecid, Benemid) 2.4 million U IM/d, plus probenecid 500 mg PO qid, both for 10–14 days

m. Penicillins
    i. Classified based on their spectra of activity
    ii. Mechanism of action: inhibition of bacterial cell growth by interference with cell wall synthesis. Binding to and activating the penicillin-binding proteins (PBPs). Exhibit time-dependent bactericidal activity and post antibiotic effect against most gram-positive organisms

iii. Clinical uses: infections of upper and lower respiratory tract, urinary tract, and central nervous system (CNS) and sexually transmitted diseases
iv. PK/PD: Most are administered parenterally (IM/IV). Widely distributed in the body and penetrate CSF
v. Excretion: Most are excreted by the kidneys; Half-life is 30 to 90 minutes,
vi. ADRs: low incidence; most common are hypersensitivity reactions

n. Penicillin benzonatate
i. MOA: bactericidal activity requires bacterial growth
ii. ADRs/interactions: antiplatelet effects, alters GI flora, impairs immunomodulatory bacterial infective agent, lowers seizure threshold.
iii. renal =adjust dose amount (CrCl 10-50: decr. dose 25% or CrCl <10: decr. dose 50-80%
iv. hepatic= HD give dose after dialysis, no supplement or PD: decr. usual dose 50-80%

o. N- Penicillin (natural PCN)
i. MOA: bactericidal; inhibits cell wall mucopeptide synthesis
ii. Metabolism: liver; CYP450: unknown
iii. Excretion: urine; Half-life: unknown
iv. Monitoring Criteria :Cr at baseline

ACRONYMS

MUC-minimal use criteria -if you see this acronym this means to use this medication or labs and imaging, it is expected you know follow up, anticipatory guidance and management of the topic. This would be considered standard of care for this topic, such as follow up labs or baseline monitoring for medications.

MEI-minimal expected criteria -when you see this acronym it means this information provided is the minimal information that is expected to be known about this topic.

SOC-standard of care- if you see this acronym it means you are held to understanding this is standard of care for this topic. If an independent reviewer (your peer) would review your care of a patient, it would be expected that you know this is the EXPECTED care every individual should receive related to diagnosis, treatment plan, follow up, expected outcomes, monitoring of the treatment plan, and anticipated guidance.

Resources

Various sources are paraphrased and combined to provide most up to date information
Arcangelo. (2020). Pharmacotherapeutics for Advanced Practice – 4th ed.
Dipiro, T., & Talbert, R. (2019). Pharmacotherapy-A pathophysiological Approach 10th ed.
Epocrates (various topics)
FamilyPracticeNotebook.com (various topics)
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Woo, T., & Wynne, A. (2021). Pharmacotherapeutics for Nurse practitioner Prescribers -5th ed.