Chapter 35: Antimicrobial Regimen Selection

INTRODUCTION

- A systematic approach to the selection and evaluation of an antimicrobial regimen is shown in **Table 35-1**. An *empiric* antimicrobial regimen is begun before the offending organism is identified and sometimes before documentation of the presence of infection, whereas a *definitive* regimen is instituted when the causative organism is known.

TABLE 35-1

Systematic Approach for Selection of Antimicrobials

Confirm the presence of infection Careful history and physical examination Signs and symptoms Predisposing factors
Identification of the pathogen (see Pharmacotherapy textbook Chapter e122.) Collection of infected material Stains Serologies Culture and sensitivity
Selection of presumptive therapy considering every infected site Host factors Drug factors
Monitor therapeutic response Clinical assessment Laboratory tests Assessment of therapeutic failure

CONFIRMING THE PRESENCE OF INFECTION

Fever

- *Fever* is defined as a controlled elevation of body temperature above the expected 37°C (98.6°F) (measured orally) and is a manifestation of many disease states other than infection.
- Many drugs have been identified as causes of fever. Drug-induced fever is defined as persistent fever in the absence of infection or other underlying condition. The fever must coincide temporally with the administration of the offending agent and disappear promptly upon its

withdrawal, after which the temperature remains normal.

White Blood Cell Count

- Most infections result in elevated white blood cell (WBC) counts (leukocytosis) because of the mobilization of granulocytes and/or lymphocytes to destroy invading microbes. Normal values for WBC counts are between 4000 and 10,000 cells/mm^3 (4×10^9 and 10×10^9/L).
- Bacterial infections are associated with elevated granulocyte counts (neutrophils and basophils), often with increased numbers of immature forms (band neutrophils) seen in peripheral blood smears. With infection, peripheral leukocyte counts may be high, but they are rarely higher than 10,000 to 40,000 cells/mm^3 (10×10^9/L to 40×10^9/L). Low neutrophil counts (neutropenia) after the onset of infection indicate an abnormal response and are generally associated with a poor prognosis for bacterial infection.
- Relative lymphocytosis, even with normal or slightly elevated total WBC counts, is generally associated with tuberculosis and viral or fungal infections. Many types of infections, however, may be accompanied by a completely normal WBC count and differential.

Local Signs

- Pain and inflammation may accompany infection and are sometimes manifested by swelling, erythema, tenderness, and purulent drainage. Unfortunately, these signs may be apparent only if the infection is superficial or in a bone or joint.
- The manifestations of inflammation with deep-seated infections such as meningitis, pneumonia, endocarditis, and urinary tract infection must be ascertained by examining tissues or fluids. For example, the presence of polymorphonuclear leukocytes (neutrophils) in spinal fluid, lung secretions (sputum), and urine is highly suggestive of bacterial infection.

IDENTIFICATION OF THE PATHOGEN

- Identification and antimicrobial susceptibility of a suspected pathogen are the most important factors in determining the choice of antimicrobial therapy.
- Infected body materials must be sampled, if at all possible or practical, before the institution of antimicrobial therapy. A Gram stain of the material may reveal bacteria, or an acid-fast stain may detect mycobacteria or actinomycetes. Premature use of antimicrobials can suppress the growth of pathogens that might result in false-negative culture results or alterations in the cellular and chemical composition of infected fluids.
- Blood cultures should be performed in the acutely ill, febrile patient. Infected materials produced by the patient (eg, blood, sputum, urine, stool, and wound or sinus drainage) and less accessible fluids or tissues are obtained when needed to assess localized signs or symptoms. Abscesses and cellulitic areas should also be aspirated.
- After a positive Gram stain, culture results, or both are obtained, the clinician must be cautious in determining whether the organism recovered is a true pathogen, a contaminant, or a part of the normal flora. Cultures of specimens from purportedly infected sites that are obtained by sampling from or through a contaminated areas might contain significant numbers of the normal flora.

SELECTION OF PRESUMPTIVE THERAPY

- A variety of factors must be considered to select rational antimicrobial therapy for a given clinical situation. These include the severity and acuity of the disease, local epidemiology and antibiogram, patient history, host factors, factors related to the drugs used, and the necessity for using multiple agents. Choice of antimicrobial is influenced by local antimicrobial susceptibility data rather than information published by other institutions or national compilations.
- The drugs of choice for the treatment of most pathogens are compiled from a variety of sources and are intended as guidelines rather than specific rules for antimicrobial use (**Table 35-2**).
- Important considerations when selecting empiric antimicrobial therapy include: (1) prior knowledge of colonization or infections, (2) previous

antimicrobial use, (3) the site of infection and the organisms most likely pathogens, and (4) local antibiogram and resistance patterns for important pathogens.

TABLE 35-2

Drugs of Choice, First Choice, *Alternative(s)*

Gram-Positive Cocci

Enterococcus faecalis (generally not as resistant to antibiotics as *Enterococcus faecium*)

- Serious infection (endocarditis, meningitis, pyelonephritis with bacteremia)
  - Ampicillin (or penicillin G) + (gentamicin or streptomycin)
  - Vancomycin + (gentamicin or streptomycin), daptomycin, linezolid, tedizolid, telavancin, tigecycline[a]
- Urinary tract infection
  - Ampicillin, amoxicillin
  - Fosfomycin or nitrofurantoin

E. faecium (generally more resistant to antibiotics than *E. faecalis*)

- Recommend consultation with infectious disease specialist
  - Linezolid, quinupristin/dalfopristin, daptomycin, tigecycline[a]

Staphylococcus aureus/*Staphylococcus epidermidis*

- Methicillin (oxacillin)-sensitive
  - Nafcillin or oxacillin
  - FGC,[b,c] trimethoprim–sulfamethoxazole, clindamycin, BL/BLI[d]
- Hospital-acquired methicillin (oxacillin)–resistant
  - Vancomycin ± (gentamicin or rifampin)
  - Ceftaroline, daptomycin, linezolid, telavancin, tigecycline,[a] trimethoprim–sulfamethoxazole, quinupristin–dalfopristin
- Community-acquired methicillin (oxacillin)–resistant
  - Clindamycin, trimethoprim–sulfamethoxazole, doxycycline[a]
  - Ceftaroline, dalbavancin, daptomycin, linezolid, oritivancin, tedizolid, telavancin, tigecycline,[a] or vancomycin

Streptococcus (groups A, B, C, G, and *Streptococcus bovis*)

- Penicillin G or V or ampicillin
- FGC,[b,c] erythromycin, azithromycin, clarithromycin

Streptococcus pneumoniae

- Penicillin-sensitive (minimal inhibitory concentration [MIC] <0.1 mcg/mL [mg/L])
  - Penicillin G or V or ampicillin
  - FGC,[b,c] doxycycline,[a] azithromycin, clarithromycin, erythromycin
- Penicillin intermediate (MIC 0.1–1 mcg/mL [mg/L])
  - High-dose penicillin (12 million units/day for adults) or ceftriaxone[c] or cefotaxime[c]
  - Levofloxacin,[a] moxifloxacin,[a] gemifloxacin,[a] or vancomycin
- Penicillin-resistant (MIC ≥1.0 mcg/mL [mg/L])
  - Recommend consultation with infectious disease specialist.
    - Vancomycin ± rifampin
    - Per sensitivities: ceftaroline, cefotaxime, ceftriaxone,[c] levofloxacin,[a] moxifloxacin,[a] or gemifloxacin[a]

Streptococcus, viridans group

- Penicillin G ± gentamicin[e]
- Cefotaxime,[c] ceftriaxone,[c] erythromycin, azithromycin, clarithromycin, or vancomycin ± gentamicin

Gram-Negative Cocci

Moraxella (Branhamella) catarrhalis

- Amoxicillin–clavulanate, ampicillin–sulbactam
- Trimethoprim–sulfamethoxazole, erythromycin, azithromycin, clarithromycin, doxycycline,[a] SGC,[c,f] cefotaxime,[c] ceftriaxone,[c] or TGCPO[c,g]

Neisseria gonorrhoeae (also give concomitant treatment for *Chlamydia trachomatis*)

- Disseminated gonococcal infection
  - Ceftriaxone[c] or cefotaxime[c]
  - Oral follow-up: cefpodoxime,[c] ciprofloxacin,[a] or levofloxacin[a]
- Uncomplicated infection
  - Ceftriaxone,[c] cefotaxime,[c] or cefpodoxime[c]
  - Ciprofloxacin[a] or levofloxacin[a]

Neisseria meningitides

- Penicillin G
- Cefotaxime[c] or ceftriaxone[c]

Gram-Positive Bacilli

Clostridium perfringens

- Penicillin G ± clindamycin
- Metronidazole,[a] clindamycin, doxycycline,[a] cefazolin,[c] carbapenem[h,i]

Clostridioides (formerly *Clostridium*) *difficile*

- Oral vancomycin or fidaxomicin
- Oral metronidazole

Gram-Negative Bacilli

Acinetobacter spp.

- Doripenem, imipenem, or meropenem ± aminoglycoside[j] (amikacin usually most effective)
- Ampicillin–sulbactam, polymyxins,[i] or tigecycline[a]

Bacteroides fragilis (and others)

- Metronidazole[a]
- BL/BLI,[d] clindamycin, cefoxitin,[c] cefotetan,[c] ceftolozane-azobactam, ceftazidime-avibactam, or carbapenem[h,i]

Enterobacter spp.

- Carbapenem[h] or cefepime ± aminoglycoside[j]
- Ceftolozane-tazobactam, ceftazidime-avibactam, ciprofloxacin,[a] levofloxacin,[a] piperacillin–tazobactam, ticarcillin–clavulanate

Escherichia coli

- Meningitis
  - Cefotaxime,[c] ceftriaxone,[c] meropenem
- Systemic infection
  - Cefotaxime[c] or ceftriaxone[c]
  - BL/BLI,[d] fluoroquinolone,[a,k] carbapenem[h,i]
- Urinary tract infection
  - Most oral agents: check sensitivities

- Ampicillin, amoxicillin–clavulanate, doxycycline,[a] or cephalexin[c]
- Aminoglycoside,[j] FGC,[b,c] nitrofurantoin, fluoroquinolone[a,k]

Gardnerella vaginalis

- Metronidazole[a]
- Clindamycin

Haemophilus influenzae

- Meningitis
  - Cefotaxime[c] or ceftriaxone[c]
  - Meropenem[i]
- Other infections
  - BL/BLI,[d] or if β-lactamase-negative, ampicillin or amoxicillin
  - Trimethoprim–sulfamethoxazole, cefuroxime,[c] azithromycin, clarithromycin, or fluoroquinolone[a,k]

Klebsiella pneumoniae

- BL/BLI,[d] cefotaxime,[c] ceftriaxone,[c] cefepime[c]
- Carbapenem,[h,i] ceftolozane-tazobactam, ceftazidime-avibactam, fluoroquinolone[a,k]

Legionella spp.

- Azithromycin, erythromycin ± rifampin, or fluoroquinolone[a,k]
- Trimethoprim–sulfamethoxazole, clarithromycin, or doxycycline[a]

Pasteurella multocida

- Penicillin G, ampicillin, amoxicillin
- Doxycycline,[a] BL/BLI,[d] trimethoprim–sulfamethoxazole or ceftriaxone[c]

Proteus mirabilis

- Ampicillin
- Trimethoprim–sulfamethoxazole

Proteus (indole-positive) (including *Providencia rettgeri*, *Morganella morganii*, and *Proteus vulgaris*)

- Cefotaxime,[c] ceftriaxone,[c] or fluoroquinolone[a,k]
- BL/BLI,[d] aztreonam,[l] aminoglycosides,[j] carbapenem,[h,i] ceftolozane-tazobactam, ceftazidime-avibactam

Providencia stuartii

- Amikacin, cefotaxime,[c] ceftriaxone,[c] fluoroquinolone[a,k]
- Trimethoprim–sulfamethoxazole, aztreonam,[l] carbapenem[h,i]

Pseudomonas aeruginosa

- Urinary tract infection only
  - Aminoglycoside[j]
  - Ciprofloxacin,[a] levofloxacin[a]
- Systemic infection
  - Cefepime,[c] ceftazidime,[c] doripenem,[i] imipenem,[i] meropenem,[i] piperacillin–tazobactam, or ticarcillin–clavulanate + aminoglycoside[j]
  - Aztreonam,[l] ceftolozane-tazobactam, ceftazidime-avibactam, ciprofloxacin,[a] levofloxacin,[a] polymyxin[i]

Salmonella typhi

- Ciprofloxacin,[a] levofloxacin,[c] ceftriaxone,[c] cefotaxime[c]

- Trimethoprim–sulfamethoxazole

Serratia marcescens

- Ceftriaxone,[c] cefotaxime,[c] cefepime,[c] ciprofloxacin,[a] levofloxacin[a]
- Aztreonam,[l] carbapenem,[h,i] piperacillin–tazobactam, ticarcillin–clavulanate

Stenotrophomonas (Xanthomonas) maltophilia (generally very resistant to all antimicrobials)

- Trimethoprim–sulfamethoxazole.
- Check sensitivities to ceftazidime,[c] doxycycline,[a] minocycline,[a] and ticarcillin–clavulanate

Miscellaneous Microorganisms

Chlamydia pneumoniae

- Doxycycline[a]
- Azithromycin, clarithromycin, erythromycin, or fluoroquinolone[a,k]

C. trachomatis

- Azithromycin or doxycycline[a]
- Levofloxacin,[a] erythromycin

Mycoplasma pneumoniae

- Azithromycin, clarithromycin, erythromycin, fluoroquinolone[a,k]
- Doxycycline[a]

Spirochetes

Treponema pallidum

- Neurosyphilis
  - Penicillin G
  - Ceftriaxone[c]
- Primary or secondary
  - Benzathine, penicillin G
  - Ceftriaxone[c] or doxycycline[a]

Borrelia burgdorferi (choice depends on stage of disease)

- Ceftriaxone[c] or cefuroxime axetil,[c] doxycycline,[a] amoxicillin
- High-dose penicillin, cefotaxime[c]

[a]Not for use in pregnant patients or children.

[b]First-generation cephalosporins—IV: cefazolin; orally: cephalexin, cephradine, or cefadroxil.

[c]Some penicillin-allergic patients may react to cephalosporins.

[d]β-Lactam/β-lactamase inhibitor combination—IV: ampicillin–sulbactam, piperacillin–tazobactam, and ticarcillin–clavulanate; orally: amoxicillin–clavulanate.

[e]Gentamicin should be added if tolerance or moderately susceptible (MIC >0.1 mcg/mL [mg/L]) organisms are encountered; streptomycin is used but can be more toxic.

[f]Second-generation cephalosporins—IV: cefuroxime; orally: cefaclor, cefditoren, cefprozil, cefuroxime axetil, and loracarbef.

[g]Third-generation cephalosporins—orally: cefdinir, cefixime, cefetamet, cefpodoxime proxetil, and ceftibuten.

[h]Carbapenem: doripenem, ertapenem, imipenem/cilastatin, and meropenem.

[i]Reserve for serious infection.

[j]Aminoglycosides: gentamicin, tobramycin, and amikacin; use per sensitivities.

[k]Fluoroquinolones IV/orally: ciprofloxacin, levofloxacin, and moxifloxacin.

[l]Generally reserved for patients with hypersensitivity reactions to penicillin.

Host Factors

- When a patient for initial or empiric therapy is evaluated, the following factors should be considered:

  ✔ Allergy or history of adverse drug reactions.

  ✔ Age of patient.

  ✔ Pregnancy.

  ✔ Metabolic or genetic variation.

  ✔ *Renal and hepatic function*: Patients with diminished renal and/or hepatic function will accumulate certain drugs unless the dosage is adjusted.

  ✔ *Concomitant drug therapy*: Any concomitant therapy the patient is receiving may influence the selection of drug therapy, the dose, and monitoring. A list of selected drug interactions involving antimicrobials is provided in **Table 35-3**.

  ✔ Concomitant disease states.

TABLE 35-3

Major Drug Interactions with Antimicrobials

Antimicrobial	Other Agent(s)	Mechanism of Action/Effect	Clinical Management
Aminoglycosides	Neuromuscular blocking agents	Additive adverse effects	Avoid
	Nephrotoxins (N) or ototoxins (O) (eg, amphotericin B [N], cisplatin [N/O], cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast [N], vancomycin [N])	Additive adverse effects	Monitor aminoglycoside SDC and renal function
Amphotericin B	Nephrotoxins (eg, aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine)	Additive adverse effects	Monitor renal function
Azoles	See Chapter 38		
Chloramphenicol	Phenytoin, tolbutamide, ethanol	Decreased metabolism of other agents	Monitor phenytoin SDC, blood glucose

Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity/hypocalcemia	Monitor renal function/serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of other agents (nausea, vomiting, nystagmus, ataxia)	Monitor drug SDC
Macrolides/Azalides	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC; avoid if possible
	Theophylline	Decreased metabolism of theophylline	Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Penicillins and cephalosporins	Probenecid, aspirin	Blocked excretion of β-lactams	Use if prolonged high concentration of β-lactam desirable
Ciprofloxacin/Norfloxacin	Theophylline	Decreased metabolism of theophylline	Monitor theophylline
Quinolones	Classes Ia and III antiarrhythmics	Increased Q-T interval	Avoid
	Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy, citric acid), didanosine	Decreased absorption of quinolone	Separate by 2 hours
Rifampin	Azoles, cyclosporine, methadone propranolol, PIs, oral contraceptives, tacrolimus, warfarin	Increased metabolism of other agent	Avoid if possible
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of other agent	Monitor blood glucose, SDC, PT
Tetracyclines	Antacids, iron, calcium, sucralfate	Decreased absorption of tetracycline	Separate by 2 hours
	Digoxin	Decreased digoxin bioavailability	Monitor digoxin SDC; avoid if possible

PI, protease inhibitor; PT, prothrombin time; SDC, serum drug concentrations.

Azalides: azithromycin; azoles: fluconazole, itraconazole, ketoconazole, and voriconazole; macrolides: erythromycin and clarithromycin; protease inhibitors: amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir; quinolones: ciprofloxacin, gemifloxacin, levofloxacin, and moxifloxacin.

Drug Factors

- Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure efficacy and prevent resistance. Antibiotics may demonstrate concentration-dependent (aminoglycosides and fluoroquinolones) or time-dependent (β-lactams) bactericidal effects.

- The importance of tissue penetration varies with the site of infection. The central nervous system (CNS) is one body site where the importance of antimicrobial penetration is relatively well defined, and correlations with clinical outcomes are established. Drugs that do not reach significant concentrations in CSF should either be avoided or instilled directly when treating meningitis.
- Apart from the bloodstream, other body fluids in which drug concentration data are clinically relevant are cerebrospinal fluid, urine, synovial fluid, and peritoneal fluid.
- Pharmacokinetic parameters such as area under the drug concentration-time curve (AUC) and maximal plasma concentration can be predictive of treatment outcome when specific ratios of AUC or maximal plasma concentration to the minimum inhibitory concentration (MIC) are achieved. For some agents, the ratio of AUC to MIC, peak-to-MIC ratio, or the time that the drug concentration is above the MIC may predict efficacy.
- The most important pharmacodynamic relationship for antimicrobials that display time-dependent bactericidal effects (such as penicillins and cephalosporins) is the duration that drug concentrations exceed the MIC.

Combination Antimicrobial Therapy

- Combinations of antimicrobials are generally used to broaden the spectrum of coverage for empiric therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.
- Increasing the coverage of antimicrobial therapy is generally necessary in mixed infections in which multiple organisms are likely to be present, such as intra-abdominal and female pelvic infections in which a variety of aerobic and anaerobic bacteria may produce disease. Combination antimicrobial therapy is also used in critically ill patients with presumed healthcare-associated infections in which an increased spectrum of activity is desirable.

Synergism

- The achievement of synergistic antimicrobial activity is advantageous for infections caused by gram-negative bacilli in immunosuppressed patients.
- Traditionally, combinations of aminoglycosides and β-lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria. However, the data supporting superior efficacy of synergistic over nonsynergistic combinations are weak.
- Synergistic combinations may produce better results in infections caused by *Pseudomonas aeruginosa*, as well as in certain infections caused by *Enterococcus* spp.
- The use of combinations to prevent the emergence of resistance is widely applied but not often realized. The only circumstance in which this has been clearly effective is in the treatment of tuberculosis.

Disadvantages of Combination Therapy

- Although there are potentially beneficial effects from combining drugs, there are also potential disadvantages, including increased cost, greater risk of drug toxicity, and superinfection with even more resistant bacteria.
- Some combinations of antimicrobials are potentially antagonistic. For example, agents that are capable of inducing β-lactamase production in bacteria (eg, cefoxitin) may antagonize the effects of enzyme-labile drugs such as penicillins or imipenem.

Monitoring Therapeutic Response

- After antimicrobial therapy has been instituted, the patient must be monitored carefully for a therapeutic response. Culture and sensitivity reports from specimens sent to the microbiology laboratory must be reviewed and the therapy changed accordingly.
- Use of agents with the narrowest spectrum of activity against identified pathogens is recommended.
- Patient monitoring should include a variety of parameters, including WBC count, body temperature, signs and symptoms of infection, appetite,

radiologic studies as appropriate, and determination of antimicrobial concentrations in body fluids.

- As the patient improves, the route of antibiotic administration should be reevaluated. Streamlining therapy from parenteral to oral (switch therapy) has become an accepted practice for many infections. Criteria favoring the switch to oral therapy include the following:

  ✔ Overall clinical improvement

  ✔ Lack of fever for 8–24 hours

  ✔ Decreased WBC

  ✔ A functioning gastrointestinal (GI) tract

Failure of Antimicrobial Therapy

- A variety of factors may be responsible for the apparent lack of response to therapy. It is possible that the disease is not infectious or nonbacterial in origin, or there is an undetected pathogen in a polymicrobial infection. Other factors include those directly related to drug selection, the host, or the pathogen. Laboratory error in identification and/or susceptibility testing errors are rare.

Failures Caused by Drug Selection

- Factors directly related to the drug selection include an inappropriate selection of drug, dosage, or route of administration. Malabsorption of a drug product due to GI disease (eg, short-bowel syndrome) or a drug interaction (eg, complexation of fluoroquinolones with multivalent cations resulting in reduced absorption) may lead to potentially subtherapeutic serum concentrations.
- Accelerated drug elimination is also a possible reason for failure and may occur in patients with cystic fibrosis or during pregnancy, when more rapid clearance or larger volumes of distribution may result in low serum concentrations, particularly for aminoglycosides.
- A common cause of failure of therapy is poor penetration into the site of infection. This is especially true for the so-called privileged sites, such as the CNS, the eye, and the prostate gland.

Failures Caused by Host Factors

- Patients who are immunosuppressed (eg, granulocytopenia from chemotherapy and acquired immunodeficiency syndrome) may respond poorly to therapy because their own defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.
- Other host factors are related to the necessity for surgical drainage of abscesses or removal of foreign bodies and/or necrotic tissue. If these situations are not corrected, they result in persistent infection and, occasionally, bacteremia, despite adequate antimicrobial therapy.

Failures Caused by Microorganisms

- Factors related to the pathogen include the development of drug resistance during therapy. Primary resistance refers to the intrinsic resistance of the pathogens producing the infection. However, acquisition of resistance during treatment has become a major problem as well.
- The increase in resistance among pathogenic organisms is believed to be due, in large part, to continued overuse of antimicrobials in the community, as well as in hospitals, and the increasing prevalence of immunosuppressed patients receiving long-term suppressive antimicrobials for the prevention of infections.

See Chapter 123, Antimicrobial Regimen Selection, authored by Grace C. Lee and David S. Burgess, for a more detailed discussion of this topic.