Chapter 127: Antimicrobial Regimen Selection

Katie B. Olney; David S. Burgess

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 35, Antimicrobial Regimen Selection.

KEY CONCEPTS

KEY CONCEPTS

1. Every attempt should be made to obtain specimens for culture and sensitivity testing prior to initiating antibiotics.

2. Empirical antibiotic therapy should be based on knowledge of likely pathogens for the site of infection, information from patient history (eg, recent hospitalizations, work-related exposure, travel, and pets), and local susceptibility.

3. Patients with delayed dermatologic reactions (ie, rash) to penicillin generally can receive cephalosporins. Patients with type I hypersensitivity reactions (ie, anaphylaxis) to penicillins should not receive cephalosporins. Alternatives to the β-lactam antimicrobials include aztreonam, quinolones, sulfonamide antibiotics, or vancomycin based on type of coverage indicated.

4. Renal function should be considered for every patient who is to receive antibiotics. Hepatic function should be considered for drugs eliminated through the hepatobiliary system, such as clindamycin, erythromycin, and metronidazole.

5. All concomitant drugs and nutritional supplements should be reviewed when an antibiotic is added to a patient's therapy to ensure drug-drug interactions will be avoided.

6. Combination antibiotic therapy may be indicated for polymicrobial infections (eg, intra-abdominal and gynecologic infections), to produce synergistic killing, or to prevent the emergence of resistance.

7. All patients receiving antibiotics should be monitored for resolution of infectious signs and symptoms (eg, decreasing temperature and white blood cell count) and adverse drug events.

8. Antibiotics with the narrowest effective spectrum of activity are preferred. Antibiotic route of administration should be evaluated daily, and conversion from IV to oral therapy should be attempted as signs of infection improve for patients with functioning GI tracts (general exceptions are endocarditis and CNS infections).

9. Patients not responding to an appropriate antibiotic treatment in 2 to 3 days should be reevaluated to ensure (a) the correct diagnosis, (b) that therapeutic drug concentrations are being achieved, (c) that the patient is not immunosuppressed, (d) that appropriate source control has been achieved (ie, abscess and foreign body), or (e) that resistance has not developed.

10. The main goals of antimicrobial stewardship programs (ASPs) are to optimize antimicrobial selection, dosing, duration, and route of administration while minimizing adverse drug events and the emergence of antimicrobial resistance.

BEYOND THE BOOK

BEYOND THE BOOK

KS is a 65-year-old woman with a past medical history significant for uterine cancer and total abdominal hysterectomy, for which they received radiation and chemotherapy. They present to the emergency department with complaints of nausea, vomiting, and flank pain. Their vital signs and laboratory values are as follows:

Laboratory Values
C-reactive protein: 224 mg/dL (2,240 mg/L)
WBC: 22,600 cells/mm^3 (22.6×10^9/L)
Bands: 10%

Vitals
Blood pressure: 95/58
Temperature: 39.4°C (103 °F)
Heart rate: 136 beats/min

1. Which of the following statements regarding microbiologic studies is false?
   A. Obtaining cultures prior to administration of antimicrobial therapy may improve culture yield.
   B. Ideally two sets of blood cultures should be obtained peripherally from two different sites 1 hour apart.
   C. Coagulase-negative staphylococci recovered from blood cultures always warrant antimicrobial treatment.
   D. Urine cultures should be evaluated in conjunction with results of the urinalysis to confirm infection.
2. Which of the following is an important consideration when selecting empiric antimicrobial therapy for this patient?
   A. Prior antimicrobial use
   B. Site of infection and the organisms most likely present
   C. Prior knowledge of colonization or infections
   D. All of the above
3. Which of the following criteria must be met prior to transitioning a patient to oral antibiotic therapy?
   A. Re-culture twice daily to ensure adequate microbiological cure
   B. Lack of fever for 8 to 24 hours

C. Resolution of electrolyte abnormalities

D. Decrease in C-reactive protein

INTRODUCTION

Antimicrobials are among the most widely used classes of drugs.[1] In the United States, expenditures for antimicrobial agents exceed $8 billion annually. Approximately 20% to 50% of inpatient antibiotic use, 40% to 75% of nursing home antibiotic use, and 30% of outpatient antibiotic use is considered unnecessary or inappropriate.[2] The use of antibiotics is the main driver in creating selective pressure for the emergence of antimicrobial resistant pathogens; nevertheless, antibiotic overuse remains common. Selecting appropriate antimicrobial agent(s) to treat an infection has proven to be a challenging task.[3] Although the choice of a single agent or a combination of agents should be individualized for each patient, certain general principles of therapy should guide the selection of specific drugs (Table 127-1).

TABLE 127-1

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 Chapter e126, “Laboratory Tests to Direct Antimicrobial Pharmacotherapy”) 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

The initial selection of antimicrobial therapy is nearly always empirical, which is prior to documentation and identification of the offending organism. Infectious diseases generally are acute, and a delay in antimicrobial therapy can result in serious morbidity or even mortality. Thus, empirical antimicrobial therapy selection should be based on information gathered from the patient’s history and physical examination and results of Gram stains or of rapidly performed tests on specimens from the infected site. This information, combined with knowledge of the most likely offending organism(s) and an institution’s local susceptibility patterns, should result in a rational selection of antibiotics to treat the patient. This chapter introduces a systematic approach to the selection of antimicrobial therapeutic regimens.

CONFIRMING THE PRESENCE OF INFECTION

An infectious disease diagnosis is determined by assessing the presence of signs and symptoms of an infection, determining the site of infection, and establishing a microbiological diagnosis, when possible.

Fever

Aberrations of temperature reaching >38°C (100.4°F) or <36°C (96.8°F) are indicative of systemic inflammation, and may often be seen in patients presenting with infectious disease processes. Body temperature is controlled by the hypothalamus. In addition, the circadian rhythm, a built-in temperature cycle, is also operational. The daily temperature rhythm can vary for each individual. In a healthy person, the internal thermostat is set between the morning low temperature and the afternoon peak as controlled by the circadian rhythm. During fever, the hypothalamus is reset at a higher temperature level.

Fever is defined as a controlled elevation of body temperature above the normal range. The average normal body temperature range taken orally is 36.7°C to 37°C (98°F–98.6°F). Body temperatures obtained rectally generally are 0.6°C (1°F) higher and axillary temperatures are 0.6°C (1°F) lower than oral temperatures, respectively. Skin temperatures are also less than the oral temperature but can vary depending on the specific measurement method. Fever can be a manifestation of disease states other than infection. Collagen vascular (autoimmune) disorders and several malignancies can have fever as a manifestation. Fever of unknown or undetermined origin is a diagnostic dilemma and is reviewed extensively elsewhere.[4]

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 on its withdrawal, after which the temperature remains normal. Possible mechanisms of drug-induced fever are either a hypersensitivity reaction or development of antigen–antibody complexes that result in the stimulation of macrophages and the release of interleukin 1 (IL-1). While fever is not a common drug effect (accounting for no more than 5% of all drug reactions), it should be suspected when obvious reasons for fever are not present. Almost any medication can produce fever, but β-lactam antibiotics, anticonvulsants, allopurinol, hydralazine, nitrofurantoin, sulfonamides, phenothiazines, and methyldopa are responsible more often than others.

Noninfectious etiologies of fever can be referred to as “false-positives.” Although these certainly can confuse the clinician, even more troublesome are false-negatives: the absence of fever in a patient with signs and symptoms consistent with an infectious disease. Careful questioning of the patient or family is vital to assess the ingestion of any medication that can mask fever (eg, aspirin, acetaminophen, nonsteroidal anti-inflammatory agents, and corticosteroids). The use of antipyretics should be discouraged during the treatment of infection unless absolutely necessary because they can mask a poor therapeutic response. Moreover, elevated body temperature, unless very high (greater than 40.5°C [105°F]), is not harmful and may be beneficial.

White Blood Cell Count

Most infections result in elevated white blood cell (WBC) counts (leukocytosis) because of the increased production and mobilization of granulocytes (neutrophils, basophils, and eosinophils), lymphocytes, or both to destroy invading microbes. The generally accepted range of normal values for WBC counts is between 4,000 and 10,000 cells/mm^3 (4×10^9 and 10×10^9/L). Values above or below this range hold important prognostic and diagnostic value.

Bacterial infections are associated with elevated granulocyte counts, often with immature forms (band neutrophils) seen in peripheral blood smears. Mature neutrophils are also referred to as *segmented neutrophils* or *polymorphonuclear* (PMN) *leukocytes*. The presence of immature forms (left shift) is an indication of an increased bone marrow response to the infection. With infection, peripheral WBC counts can be very high, but they are rarely higher than 30,000 to 40,000 cells/mm^3 (30×10^9/L to 40×10^9/L). Because leukocytosis indicates the normal host response to infection, low leukocyte counts after the onset of infection indicate an abnormal response and generally are associated with a poor prognosis.

The most common granulocyte defect is neutropenia, a decrease in absolute numbers of circulating neutrophils. A thorough description of the consequences of neutropenia is given in Chapter 145, “Infections in Immunocompromised Patients.” Lymphocytosis, even with normal or slightly elevated total WBC counts, generally is associated with tuberculosis and viral or fungal infections. Increases in monocytes can be associated with tuberculosis or lymphoma, and increases in eosinophils can be associated with allergic reactions to drugs or infections caused by metazoa. Many types of infections can be accompanied by a completely normal WBC count and differential.

Local Signs

The classic signs of pain and inflammation can manifest as swelling, erythema, tenderness, and purulent drainage. Unfortunately, these are only visible if the infection is superficial or in a bone or joint. The manifestations of inflammation in deep-seated infections (eg, meningitis, pneumonia,

endocarditis, and urinary tract infection) must be ascertained by examining tissues or fluids. For example, the presence of neutrophils in spinal fluid, lung secretions (sputum), or urine is highly suggestive of a bacterial infection.

Symptoms referable to an organ system must be sought out carefully because not only do they help in establishing the presence of infection, but they also aid in narrowing the list of potential pathogens. For example, a febrile patient with complaints of flank pain and dysuria may be presenting with pyelonephritis. In this situation, enteric gram-negative bacilli, especially *Escherichia coli*, are the predominant pathogens. If a febrile patient has no symptoms suggestive of an organ system but only constitutional complaints, the list of possible infectious diseases is lengthy.[4] A febrile individual with cough and sputum production may have a pulmonary infection. What is not so evident, however, is the etiologic organism in this situation, because pneumonia can be bacterial, viral, or fungal in etiology.[5] In this situation, attention to the patient's history and background disease states is important. Even more important is a careful examination of the infected material (in this case sputum) to ascertain the identity of the pathogen.

IDENTIFICATION OF THE PATHOGEN

Microbiological Studies

1 Identification and antimicrobial susceptibility of a pathogen are the most important factors in determining the choice of antimicrobial therapy. Generally, infected body materials must be sampled, if at all possible or practical, before or concurrently with institution of any antimicrobial therapy for two reasons. First, a Gram stain of the material might reveal bacteria, or an acid-fast stain might detect mycobacteria or actinomycetes. Second, the premature use of antimicrobials can suppress the growth of pathogens that might result in false-negative cultures results or alterations in the cellular and chemical composition of infected fluids. This is particularly true in patients with vertebral osteomyelitis, urinary tract infections, subacute endocarditis, meningitis, and septic arthritis.[11]

Blood cultures should be performed in the acutely ill febrile patient. Blood culture collection should coincide with sharp elevations in temperature, suggesting the possibility of microorganisms or microbial antigens in the bloodstream. Ideally, blood should be obtained from peripheral sites as two sets (one set consists of an aerobic bottle and one set an anaerobic bottle) from two different sites approximately 1 hour apart to optimize culture yield. In selected infections, bacteremia is qualitatively continuous (eg, endocarditis), so cultures can be obtained at any time.[10]

In addition to the infected materials produced by the patient (eg, blood, sputum, urine, stool, and wound or sinus drainage), other less accessible fluids or tissues must be obtained if they are suspected to be the infected site (eg, spinal fluid in meningitis and joint fluid in arthritis). Abscesses and cellulitic areas also should be aspirated.

When a pathogenic microorganism is identified, the next step for the majority of clinical microbiological laboratories is antimicrobial susceptibility testing (AST) that measures the ability of a select organism to grow in the presence of an antimicrobial agent. These methods are described in detail in Chapter e126. Once a microorganism is identified and its susceptibilities are known, antimicrobial therapy should be tailored to the specific pathogen.

Over the last decade, there has been an explosion in the development of rapid diagnostic methods that provide simultaneous organism identification and resistance marker detection. These methods include nonamplified probe technologies (peptide nucleic-acid-fluorescence in situ hybridization), proteomics, and nucleic acid amplification methods combined with microarray technologies. These tests can significantly reduce time to organism identification, thereby reducing time to effective antimicrobial therapy. Rapid diagnostic tests reduce overall antimicrobial use, length of hospital stay, and mortality among patients with infectious diseases.[12-16]

Interpreting Results

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 (see Chapter e126). The latter consideration is especially problematic with cultures obtained from the skin, oropharynx, nose, ears, eyes, throat, and perineum. These surfaces are heavily colonized with a wide variety of bacteria, some of which can be pathogenic in certain settings. For example, coagulase-negative staphylococci are found in cultures of all the aforementioned sites, yet are seldom regarded as pathogens unless recovered from multiple blood cultures, venous access catheters, or prosthetic devices.

Cultures of specimens from purportedly infected sites that are obtained by sampling from or through one of these contaminated areas might contain significant numbers of the normal flora. For example, asymptomatic bacteriuria, or bacterial colonization of the genitourinary tract in the absence of

symptoms, is common even in healthy individuals. The treatment of asymptomatic bacteriuria is an important contributor to inappropriate antimicrobial use and promotion of resistance.[17] Careful consideration of a patient's presenting symptoms, risk factors, and history are essential to discern true infection from colonization..

Particularly problematic are expectorated sputum specimens that must be evaluated carefully by determination of the presence of squamous epithelial cells and leukocytes.[4] A predominance of epithelial cells in sputum specimens reduces the likelihood that recovered bacteria are pathogenic, especially when multiple types of organisms are seen on Gram stain. In contrast, the discovery of leukocytes in large numbers with one predominant type of organism is a more reliable indicator of a valid collection and quality sample. In general, however, sputum evaluation has poor sensitivity and specificity as a diagnostic test.[5]

Gram-staining techniques, culture methods, and serologic identification, as well as susceptibility testing, are discussed in detail in Chapter e126. Emphasis must be placed on the proper collection and handling of specimens and careful assessment of Gram stain or other test results in guiding the clinician toward appropriate selection of initial antimicrobial therapy.[18]

SELECTION OF PRESUMPTIVE THERAPY

In many instances, empiric therapy must be instituted before microbiological results are available. To select rational antimicrobial therapy for a given clinical situation, a variety of factors must be considered. 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. In addition, there are generally accepted drugs of choice for the treatment of most pathogens (see Appendix 127-1).

Antibiogram

Drugs of choice are compiled from a variety of sources and are intended as guidelines rather than as specific rules for antimicrobial use. These choices are influenced by local antimicrobial susceptibility data rather than information published by other institutions or national compilations. Each institution should publish an annual summary of antibiotic susceptibilities (antibiogram) for organisms cultured from patients. Antibiograms contain both the number of nonduplicate isolates for common species and the percentage susceptible to the antibiotics tested. To further guide empirical antibiotic therapy, some hospitals publish unit-specific antibiograms in unique patient care areas, such as intensive care units or burn units.

Susceptibility of bacteria can differ substantially among hospitals within a community. For example, the prevalence of hospital-acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA) in some centers is quite high, whereas in other centers the problem might be nonexistent. This particular situation will influence the selection of therapy for possible *S. aureus* infection, where the clinician must choose either a β-lactam or vancomycin. The problem of differing susceptibilities is not limited only to gram-positive bacteria but also is evident in gram-negative organisms, and all drug classes are affected.

Patient History

Empirical therapy is directed at organisms that are known to cause the infection in question. These organisms are discussed for different sites of infection in Chapters 124–143. To define the most likely infecting organisms, a careful history and physical examination must be performed. The place where the infection was acquired should be determined, for example, the home (community acquired), nursing home environment, or hospital acquired (nosocomial). Nursing home patients can be exposed to potentially more resistant organisms because they are often surrounded by ill patients who are receiving antibiotics. Important considerations when selecting empiric antimicrobial therapy include: (1) prior knowledge of colonization or infections, (2) previous antimicrobial exposure, (3) the site of infection and the most likely pathogens, and (4) local antibiogram and resistance patterns for important pathogens. Other questions to ask infected patients regarding the history of present illness include: (1) Are any other people sick at home, especially children? (2) Are any unusual pets kept in the home? (3) Where are you employed (ie, are you exposed to contaminated meat or infectious biohazards)? and (4) Has there been any recent travel (ie, to endemic areas of fungal infections or developing countries)?

Host Factors

Several host factors should be considered when evaluating a patient for antimicrobial therapy. The most important factors are drug allergies, age, pregnancy, genetic or metabolic abnormalities, renal and hepatic function, site of infection, concomitant drug therapy, and underlying disease states.

Allergy

Anaphylactic allergy to an antimicrobial agent generally precludes its use. Careful assessment of allergy histories must be performed because many patients confuse common adverse drug effects (ie, GI disturbance) with true allergic reactions.[19-21] Among the most commonly cited antimicrobial allergies are those to penicillin, penicillin-related compounds, or both. In the absence of complete penicillin skin testing capabilities, a rule of thumb for giving cephalosporins to patients allergic to penicillin is to avoid giving them to patients who give a good history for immediate or accelerated reactions (eg, anaphylaxis, laryngospasm) and to give them under close supervision in patients with a history of delayed reactions, such as a rash.[19] If a gram-negative infection is suspected or documented, therapy with a monobactam may be appropriate because cross-reactivity with other β-lactams is nonexistent, with the exception of isolated cross-reactivity in ceftazidime-allergic patients.

Age

The patient's age is an important factor both in identifying the likely etiologic organism and in assessing pharmacokinetic alterations that may impact the patient's ability to eliminate the drug(s) to be used. The best example of an age determinant of organisms is in bacterial meningitis, where the pathogens differ as the patient grows from the neonatal period through infancy and childhood into adulthood.[6,7]

The impact of age on pharmacokinetics is exemplified in the neonatal population. Neonates have several pharmacokinetic alterations that may lead to variations in drug absorption, distribution, and metabolism. At birth, infants have reduced phase I (eg, cytochrome P450 enzymatic) and phase II (eg, glucuronidation and acetylation) metabolism that develops rapidly throughout the first year of life. Phase II metabolism occurs primarily through sulfation from birth through the first few months of life and is eventually replaced by glucuronidation and acetylation. In addition, neonates have more body water content that results in a larger volume of distribution and variations in gastric emptying time leading to alterations in drug absorption. Each of these alterations result in the need for adjustments in antibiotic dosing regimens.[22] Additional special drug considerations for pediatric patients include availability of dosage formulations (eg, concentration of liquid dosage forms and availability of tablet strengths) and compliance-enhancing features (eg, palatability).

The major physiologic change in persons older than 65 years of age is a decline in the number of functioning nephrons that, in turn, results in decreased renal function.[23] This is usually manifested by an increased incidence of side effects caused by antimicrobials that are eliminated renally.

Pregnancy

During pregnancy, not only is the fetus at risk for drug teratogenicity, but the pharmacokinetic disposition of certain drugs can be altered.[24-27] Penicillins, cephalosporins, and aminoglycosides are cleared from the peripheral circulation more rapidly during pregnancy. This is probably a result of marked increases in intravascular volume, glomerular filtration rate, and hepatic and metabolic activities. The net result is that maternal serum antimicrobial concentrations can be as much as 50% lower during this period than in the nonpregnant state. Increased dosages of certain compounds might be necessary to achieve therapeutic levels during late pregnancy.[26]

Metabolic or Genetic Variation

Inherited or acquired metabolic abnormalities will influence the therapy of infectious diseases in a variety of ways. For example, patients with impaired peripheral vascular flow may not absorb drugs given by intramuscular injection. In addition, certain metabolic states can predispose patients to enhanced drug toxicity. For instance, patients who are phenotypically slow acetylators of isoniazid are at greater risk for peripheral neuropathy.[28] Patients with severe deficiency of glucose-6-phosphate dehydrogenase can develop significant hemolysis when exposed to such drugs as sulfonamides, nitrofurantoin, nalidixic acid, antimalarials, and dapsone. Although mild deficiencies are found in African Americans, the more severe forms of the disease generally are confined to persons of eastern Mediterranean origin. Another example is the antiretroviral drug abacavir, which is associated with a severe hypersensitivity reaction, consisting of fever, rash, abdominal pain, and respiratory distress. This risk has been associated with the presence of a human leukocyte antigen allele HLA-B*5701. Routine screening for the presence of this allele before initiating treatment with abacavir is a recommendation in the current HIV treatment guidelines. Furthermore, the hepatic cytochrome P450 system is a major pathway for a large number of antimicrobials. While differential host expressions of these enzymes occur, insufficient clinical data are available to recommend routine screening for antimicrobial therapy.

Organ Dysfunction

4 Patients with diminished renal or hepatic function may have pharmacokinetic alterations resulting in altered antibiotic exposure. These alterations often necessitate dose individualization and therapeutic drug monitoring, especially in critically ill populations. Because many of the commonly used antimicrobials are primarily cleared by the kidneys, it is imperative to adjust the dosing regimen as clinically appropriate.[29,30] However, there are many etiologies for altered serum creatinine concentrations aside from renal dysfunction (eg, sepsis, immobility-related cachexia) and inappropriate assessment of these concentrations may lead to inaccurate estimations of glomerular filtration rate (GFR) and creatinine clearance (CrCl).[31] Renal dose adjustment of antibiotics should be delayed for the first 48 hours of illness in patients admitted with acute kidney injury (AKI) being treated for infectious diseases.[32] Clinicians should always consider patient-specific factors, severity of illness, and pathogens of concern when making dose adjustments based on measured serum creatinine concentrations. Nephrotoxic medications (eg, aminoglycosides) are generally avoided in patients with severe liver disease.[33]

Concomitant Drugs

5 Any concomitant therapy that the patient is receiving can influence the drug selection, dose, and monitoring. For instance, administration of isoniazid to a patient who is also receiving phenytoin can result in phenytoin toxicity secondary to inhibition of phenytoin metabolism by isoniazid. Furthermore, drugs that possess similar adverse effect profiles can increase the risk for effects (ie, two drugs that cause nephrotoxicity or neutropenia). A detailed review of drug interactions is beyond the scope of this chapter, but an excellent textbook on this subject is available.[34] Lists of potentially severe drug-drug interactions are provided in Table 127-2.

TABLE 127-2

Major Drug–Drug Interactions with Antimicrobials

Antimicrobial	Interacting Agent(s)	Mechanism of Action/Effect	Clinical Management
Aminoglycosides	Neuromuscular blocking agents	Additive toxicity of neuromuscular-blocking agents	Monitor therapy
	Nephrotoxins (N) or ototoxins (O) (eg, amphotericin B [N], cisplatin [N/O], cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast [N], vancomycin [N])	Additive toxicity	Monitor renal function, obtain regular audiograms for patients receiving prolonged or repeated courses of aminoglycosides
	β-lactams	Aminoglycoside degradation	Separate administration and flush line thoroughly between doses of aminoglycoside and β-lactam therapy
Amphotericin B	Nephrotoxins (eg, aminoglycosides, cyclosporine, foscarnet)	Additive nephrotoxicity	Monitor renal function
Azoles	See Chapter 144		
Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity and hypocalcemia	Monitor renal function and serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of carbamazepine and phenytoin, resulting in increased serum concentrations	Monitor for signs and symptoms of phenytoin and carbamazepine and phenytoin toxicity (eg, nausea, vomiting, nystagmus, ataxia)

Macrolides/azalides	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC
	Theophylline	Decreased metabolism of theophylline	Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Fluoroquinolones	Other QTc-prolonging agents (eg, antiemetics, macrolides, azoles, antidepressants, etc.)	Prolonged QTc interval	Monitor ECG at baseline and periodically while on concomitant QTc-prolonging therapy
	Multivalent cations	Decreased absorption of fluoroquinolone	Separate administration by at least 2 hours
Rifampin	Azoles, cyclosporine, methadone, propranolol, oral contraceptives, tacrolimus, warfarin	Increased of metabolism of interacting agent via rifampin induction of CYP-450 metabolism resulting in decreased serum concentrations	Avoid
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of interacting agent resulting in increased serum concentrations	Monitor blood glucose, SDC of interacting agent, and PT
Doxycycline	Multivalent cations	Decreased absorption of tetracycline	Separate administration by at least 2 hours

Concomitant Disease States

Concomitant disease states can influence the selection of therapy. Certain diseases will predispose patients to a particular infectious disease or will alter the type of infecting organism. For example, patients with diabetes mellitus and resulting peripheral vascular disease often develop infections of the lower extremity soft tissue. Moreover, the alterations in peripheral blood flow associated with the disease and perhaps altered immunity make such infections more difficult to treat than in nondiabetics. Patients with chronic lung disease or cystic fibrosis develop frequent pulmonary infections that can be caused by somewhat different microorganisms than are found in otherwise normal hosts.

Patients with immunosuppressive diseases, such as malignancies or acquired immunologic deficiencies, are highly predisposed to infections, and the types of causative or pathogenic organisms can be vastly different from what would be expected (see Chapter 145, “Infections in Immunocompromised Patients”). For instance, patients undergoing chemotherapy for acute forms of leukemia often are profoundly granulocytopenic and are predisposed to infections caused by bacteria and fungi.[35] Patients with acquired immunodeficiency syndrome (AIDS) are more likely to become infected with less common opportunistic pathogens (see Chapter 148, “Human Immunodeficiency Virus”). Many factors predisposing to infection are related to disruption of the host’s integumentary barriers. For example, trauma, burns, and iatrogenic wounds induced in surgery can lead to a substantial risk of infection depending on the severity and location of the injury or disruption. For a complete discussion of the various risks involved in surgical procedures, see Chapter 146, “Antimicrobial Prophylaxis in Surgery.”

DRUG FACTORS

Pharmacokinetic and Pharmacodynamic Considerations

Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure

efficacy and to prevent resistance.[36] Early researchers relied solely on pharmacokinetic properties such as the area under the (drug concentration) curve (AUC), maximum observed concentration (peak), and drug half-life to optimize therapy. Pharmacodynamics is the study of the relationship between drug concentration and the effects on the microorganism. There is an important relationship between both pharmacokinetic and microbiologic parameters that has resulted in measurements such as AUC:minimal inhibitory concentration (MIC) ratio, peak:MIC ratio, and time (*T*) the concentration is above MIC (*T* > MIC).[37-41]

Aminoglycosides exhibit concentration-dependent bactericidal effects. An example of the integration of pharmacokinetics and microbiologic activity is the use of high-dose, once-daily aminoglycosides. For these regimens, the drug is given as a single large daily dose to maximize the peak:MIC ratio. Aminoglycosides also possess a post-antibiotic effect (persistent suppression of organism growth after concentrations decrease below the MIC) that contribute to the success of high-dose, once-daily administration. Fluoroquinolones exhibit concentration-dependent killing activity, but optimal killing is characterized by the AUC:MIC ratio.

β-Lactams display time-dependent bactericidal effects. Killing activity is enhanced only marginally if drug concentration exceeds the MIC. Therefore, the important pharmacodynamic relationship for these antimicrobials is the duration that drug concentrations exceed the MIC (*T* > MIC). Effective dosing regimens require serum drug concentrations to exceed the MIC for at least 40% to 60% of the dosing interval. *In vitro*, *in vivo* animal, and human clinical trials have demonstrated improved pharmacodynamic attainment and clinical efficacy with continuous or prolonged infusions of β-lactams.[37] A detailed discussion on antimicrobial pharmacokinetics–pharmacodynamics is beyond the scope of this chapter. However, excellent sources of information on this topic are available.[36,42,43]

Tissue Penetration

The importance of tissue penetration varies with site of infection. Some of the difficulties in interpreting data include a lack of correlation with clinical outcomes and poor understanding of whether the antimicrobial agents are present in a biologically active form. An example of the former problem is the recognized efficacy of drugs with low biliary fluid concentrations in the treatment of cholecystitis, cholangitis, or both and the absence of the enhanced efficacy of drugs whose primary route of elimination is biliary excretion of active drug. An example of the latter difficulty is with penetration to deep infections, such as abscesses, where various factors such as acid pH, WBC products, and various enzymes can inactivate even high concentrations of certain drugs. The CNS is one body site where antimicrobial penetration is relatively well defined, and correlations with clinical outcomes are established.[6,11,44] Cerebrospinal fluid (CSF) concentrations of antimicrobial agents necessary to cure bacterial meningitis have been defined, and drugs that do not reach significant concentrations in the CSF should be either avoided or instilled directly, if feasible. Caution must be exercised when selecting an antimicrobial agent for clinical use on the basis of tissue or fluid penetration. Body fluids where drug concentration data are clinically relevant include CSF, urine, ocular, synovial fluid, and peritoneal fluid. More attention should be paid to clinical efficacy, antimicrobial spectrum, and toxicity than to comparative data on penetration into a given body site.

The proper route of administration for an antimicrobial depends on the site of infection. Parenteral therapy is warranted when patients are being treated for febrile neutropenia or deep-seated infections such as meningitis, endocarditis, and osteomyelitis. Severe pneumonia often is treated initially with IV antibiotics and switched to oral therapy as clinical improvement is evident.[5,22,45] Patients treated in the ambulatory setting for bacterial upper respiratory tract infections (eg, pharyngitis, bronchitis, sinusitis, and otitis media), lower respiratory tract infections, skin and soft-tissue infections, uncomplicated urinary tract infections, and selected sexually transmitted diseases can usually receive oral therapy.

Drug Toxicity

It is incumbent on health professionals to avoid toxic drugs whenever possible. Antibiotics associated with CNS toxicities, usually when not dose-adjusted for renal function, include penicillins, cephalosporins, quinolones, and imipenem. Hematologic toxicities generally are manifested with prolonged use of β-lactam antimicrobials, vancomycin, or sulfamethoxazole/trimethoprim. Reversible nephrotoxicity classically is associated with aminoglycosides and vancomycin. Irreversible ototoxicity can occur with aminoglycosides. In the outpatient setting, patients must be counseled regarding photosensitivity with azithromycin, quinolones, tetracyclines, pyrazinamide, and sulfamethoxazole/trimethoprim. Lastly, all antibiotics have been implicated in causing diarrhea and colitis secondary to *Clostridium difficile* (see Chapter 136, "Gastrointestinal Infections and Enterotoxigenic Poisonings").[46] List of potential antibiotic adverse drug reactions is provided in Table 127-3.

TABLE 127-3

Antimicrobial Adverse Drug Reactions

Antimicrobial Class	Adverse Drug Reaction	Monitoring Parameters	Comments
Penicillins	Rash, N/V/D, hypersensitivity reactions including anaphylaxis, LFT elevations, interstitial nephritis, cytopenias, hemorrhagic cystitis, *C. difficile* colitis	• Hypersensitivity reactions (eg, bronchospasm, anaphylaxis) • CBC with differential • Renal function • Hepatic function	Immediate IgE-mediated anaphylaxis incidence is <0.05%.
Cephalosporins	Rash, N/V/D, hypersensitivity reactions including anaphylaxis, LFT elevations, interstitial nephritis, cytopenias, Coomb's positive hemolytic anemia, *C. difficile* colitis	• Hypersensitivity reactions (eg, bronchospasm, anaphylaxis) • CBC with differential • Renal function • Hepatic function	
Carbapenems	Rash, N/V/D, hypersensitivity reactions including anaphylaxis, LFT elevations, interstitial nephritis, cytopenias, eosinophilia, *C. difficile* colitis	• Hypersensitivity reactions (eg, bronchospasm, anaphylaxis) • CBC with differential • Renal function • Hepatic function	Clinically significant cross-sensitivity reactions in penicillin-allergic patients reported to be as low as 1%. Incidence of seizures more frequent in patients who are elderly, have history of seizure disorders, or who have renal dysfunction.
Monobactams	Rash, diarrhea, nausea, LFT elevations, *C. difficile* colitis, thrombocytopenia	• CBC with differential • Renal function • Hepatic function	May be used in patients with anaphylactic penicillin allergy. *Note:* Isolated cross-reactivity has been described in ceftazidime-allergic patients due to a shared R-side chain.
Aminoglycosides	Tubular necrosis and renal failure (reversible), vestibular and cochlear toxicity, anemia, hypersensitivity	• Renal function (daily) • SDC • Obtain regular audiology exams in patients with prolonged or cumulative exposure to aminoglycosides	Nephrotoxicity is more common in patients with the following risk factors: elderly, history of renal dysfunction, concomitant administration of nephrotoxic drugs, and prolonged duration of therapy. Ototoxicity can be irreversible.

Glycopeptides	Red person syndrome, phlebitis, renal dysfunction, neutropenia, leukopenia, eosinophilia, thrombocytopenia, drug fever	• Renal function • SDC • CBC with differential if on prolonged therapy	Red person syndrome is associated with rapid infusion and nonspecific histamine release; prolonging vancomycin infusion and pre-medicating with antihistamines often mitigates occurrence.
Lipopeptides	Elevations in serum creatinine phosphokinase (CPK) levels, rhabdomyolysis, eosinophilic pneumonia.	• Renal function • CPK at baseline and weekly (or more frequently in patients with prior or concomitant statin, renal dysfunction, or patients with baseline elevations in CPK)	Daptomycin doses should be held in the setting of: (1) CPK elevation >5× the upper limit of normal (ULN) in patients who have symptoms of rhabdomyolysis or (2) CPK elevation >10× the ULN in patients who are asymptomatic. Daptomycin may be restarted if CPK level returns to baseline.
Oxazolidinones	Myelosuppression (thrombocytopenia, leukopenia, and anemia), peripheral neuropathy, optic neuropathy, lactic acidosis, diarrhea, nausea, serotonin syndrome	• Monitor for signs and symptoms of serotonin syndrome in patients receiving concomitant serotonergic agents • CBC with differential • For prolonged therapy, monitor visual acuity	Myelosuppression is reversible and associated with treatment duration >2 weeks.
Tetracyclines	GI upset, N/V/D, hepatotoxicity, esophageal ulcerations, photosensitivity, azotemia, visual disturbances, vertigo, hyperpigmentation, hemolytic anemia, pseudotumor cerebri, pancreatitis, *C. difficile* colitis	• CBC with differential • Renal function • Hepatic function	Vestibular symptoms more frequent in women than in men. Avoid use during pregnancy. The American Academy of Pediatrics (AAP) provides guidance on utilization of doxycycline in pediatrics: doxycycline may be used ***without regard to patient age*** for treatment durations ≤21 days.
Chloramphenicol	Myelosuppression, aplastic anemia, "gray baby syndrome," optic neuritis, peripheral neuropathy, digital paresthesias, GI upset, *C. difficile* colitis, hypersensitivity reactions	• CBC with differential (baseline and daily) • Renal function • Hepatic function • SDC (particularly in	Bone marrow suppression associated with doses >4 g/day. Use has fallen out of favor due to significant toxicities.

		children and in patients with hepatic or renal insufficiency)	
Rifamycines	Red discoloration of urine, tears, contact lens, sweat, hepatotoxicity, GI upset, flu-like syndrome, hypersensitivity, thrombocytopenia, leukopenia, drug fever, interstitial nephritis	• CBC with differential (baseline and daily) • Renal function • Hepatic function (LFTs, bilirubin)	Increased potential for hepatitis with concomitant hepatotoxic drugs (ie, TB drugs).
Macrolides/azalide	GI intolerance, diarrhea, prolonged QTc, cholestatic hepatitis, reversible ototoxicity, torsade de pointes, rash, hypothermia, exacerbation of myasthenia gravis	• Hepatic function in high-risk patients • ECG (baseline and periodically if on multiple QTc-prolonging agents or if prolonged QTc at baseline)	
Clindamycin	Diarrhea, *C. difficile* colitis, nausea, vomiting, generalized rash, hypersensitivity	• Signs/symptoms of *C. difficile* • Hepatic function (if prolonged therapy)	
Fluoroquinolones	GI intolerance, headache, malaise, insomnia, dizziness, photosensitivity, QTc prolongation, tendon rupture, peripheral neuropathy, crystalluria, seizure, interstitial nephritis, Stevens-Johnson syndrome, allergic pneumonitis, *C. difficile* colitis	• Renal function • Signs and symptoms of encephalopathic changes (eg, confusion, hallucinations, and tremor)	Tendon rupture more frequently seen in the elderly and kidney, heart, and lung transplant recipients, and with concurrent use of corticosteroids.
Polymyxins	Nephrotoxicity, neurotoxicity (paresthesia, vertigo, ataxia, blur red vision, slurred speech), neuromuscular blockade, bronchospasms (when administered via inhalation)	• CBC with differential (baseline and daily) • Renal function (baseline and daily) • Signs of neurotoxicity (eg, peripheral paresthesias, blurred vision, apnea, muscle	Nephrotoxicity is dose-dependent.

		weakness)	
Sulfonamides and trimethoprim	GI intolerance, rash, hyperkalemia, bone marrow suppression (eg, anemia with folate deficiency, thrombocytopenia, and leukopenia), serum sickness, hepatitis, photosensitivity, crystalluria with azotemia, urolithiasis, methemoglobinemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, pancreatitis, interstitial nephritis	• Hypersensitivity reactions (eg, bronchospasm, anaphylaxis) and rash • CBC with differential • Renal function • Hepatic function • Serum potassium	HIV-infected patients are at increased risk for developing adverse drug reactions. Methemoglobinemia due to severe G6PD deficiency.
Metronidazole	N/V/D, headache, metallic taste, dark urine, peripheral neuropathy, disulfiram reactions with alcohol, insomnia, stomatitis, dysarthria	• CBC with differential (baseline and periodically during prolonged therapy) • Hepatic function • Signs of neurotoxicity	Peripheral neuropathy is reversible and associated with prolonged treatment.

CBC, complete blood count; CPK, creatine phosphokinase; LFT, liver function test; SDC, serum drug concentrations; TB, tuberculosis.

Aside from consideration of drug toxicity, some antimicrobial use requires more intensive risk–benefit analysis. An example of this is the decision to use isoniazid for treatment of latent tuberculosis. Because the hepatotoxicity of isoniazid increases in frequency with age, older persons (greater than 45 years of age) who have latent tuberculosis must have additional risk factors for tuberculosis to balance the potential toxic effects. These include immunosuppression, or immunocompromising conditions, including HIV. Older patients without additional risk factors are more likely to suffer toxicity from isoniazid than derive benefit from its use.

COMBINATION ANTIMICROBIAL THERAPY

6 In selecting a drug regimen for a given patient, consideration must be given to the necessity of using more than one drug empirically. Inappropriate or inadequate antimicrobial therapy has been associated with increased morbidity and mortality.[47] Combinations of antimicrobials generally are used to broaden the spectrum of coverage for empirical therapy, achieve synergistic activity against the infecting organism, and mitigate the emergence of resistance.[48,49]

Broadening the Spectrum of Coverage

Increasing the coverage of antimicrobial therapy generally is necessary in two scenarios. The first scenario is in mixed infections where multiple organisms are likely to be present. This is the case in intra-abdominal and female pelvic infections, in which a variety of aerobic and anaerobic bacteria can produce disease.[50] Traditionally, a combination of a drug active against aerobic gram-negative bacilli (such as an aminoglycoside) and a drug active against anaerobic bacteria (such as metronidazole) is selected. Options for monotherapy which possess good activity against both of these types of organisms, include the β-lactam/β-lactamase inhibitor combinations and carbapenems. The second scenario is for critically ill patients with presumed healthcare-associated infections in which an increased spectrum of activity is desirable.[45] Healthcare-associated infections are frequently caused by multi-drug resistant pathogens; combination therapy is often used in this setting to ensure that at least one of the antimicrobials will be

active against the pathogen(s).

Synergism

The achievement of synergistic antimicrobial activity is advantageous for some serious bacterial infections. Laboratory tests to identify synergy between antibiotic combinations are described in Chapter e126. 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. At best, synergistic combinations produce better results in infections caused by *Enterococcus* species.[42-44]

The most obvious example of the use of synergy is the treatment of enterococcal endocarditis. The causative organism is usually only inhibited by penicillins, but it is killed rapidly by the addition of gentamicin or ceftriaxone to a penicillin. The need for bactericidal activity in the treatment of endocarditis underscores the need for these synergistic combinations.[9,10]

Preventing Resistance

The use of antimicrobial combinations to prevent the emergence of resistance is applied widely but not often realized. The only circumstance where this has been clearly effective is in the treatment of tuberculosis. The prevalence of resistance to a first-line drug such as isoniazid or rifampin in a population of organisms may be as high as 1 in 10^6 to 10^8. Because the bacterial load in a patient with active tuberculosis often exceeds this, two drugs are given to reduce the likelihood of encountering resistance to less than 1 in 10. There is ample evidence from *in vitro* data and experimental bacterial infections that combinations of drugs with different mechanisms are effective in the prevention of the emergence of resistance.

Disadvantages of Combination Therapy

Although there are potentially beneficial effects from combining drugs, there also are potential disadvantages, including increased cost, greater risk of drug toxicity, and superinfection with even more resistant bacteria.[9,51]The combination of two or more antibiotics can result in antagonistic effects. For example, the effect of antagonism may be evident when one drug induces β-lactamase production and another drug is β-lactamase unstable.

MONITORING THERAPEUTIC RESPONSE

7 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. If anaerobes are suspected, even if they are not identified, anti-anaerobic therapy should be continued.

Patient monitoring should include many of the same parameters used to diagnose the infection. The WBC count and temperature should start to normalize. Physical complaints from the patient also should diminish (ie, decreased pain, shortness of breath, cough, or sputum production). Appetite should improve. However, radiologic improvement can lag behind clinical improvement.

Determinations of serum (or other fluid) levels of antimicrobials can be useful in ensuring outcome, preventing toxicity, or both. Vancomycin, aminoglycosides, and voriconazole are examples of antimicrobials that require routine monitoring of serum concentrations. Achievement of adequate aminoglycoside concentrations within the first few days of therapy of gram-negative infection has been correlated with better therapeutic outcome.[52]

Changes in the volume of distribution can have a significant impact on the efficacy and safety of therapy. An unexpectedly low volume of distribution (such as in the dehydrated patient) will result in higher, potentially toxic drug concentrations, whereas a larger-than-expected volume of distribution (such as in patients with edema or ascites) will result in low, potentially subtherapeutic concentrations. The most effective methods use measured serum concentrations of the drugs rather than estimations from renal function tests to assess true drug clearance from the body.

8 As patients improve clinically, the route of administration should be reevaluated. Transitioning therapy from parenteral to oral (step-downtherapy) has become an accepted practice for many infections.[5,22] Criteria that should be present to justify a switch to oral therapy include (a) overall clinical improvement, (b) lack of fever for 8 to 24 hours, (c) decreased WBC count, and (d) a functioning GI tract. Drugs that exhibit excellent oral

bioavailability when compared with IV formulations include fluoroquinolones, clindamycin, doxycycline, metronidazole, linezolid, and trimethoprim–sulfamethoxazole.

FAILURE OF ANTIMICROBIAL THERAPY

A variety of factors may be responsible for an apparent lack of response to therapy. Patients who fail to respond over 2 to 3 days require a thorough reevaluation. It is possible that the disease is not infectious or is not bacterial 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, susceptibility testing, or both (presence of inoculum effect or resistant subpopulations) is a rare cause of antimicrobial failure.

Failures Caused by Drug Selection

Factors related directly to the drug selection include an inappropriate drug selection, dosage, or route of administration. Malabsorption of a drug product because of GI disease (such as a short-bowel syndrome) or a drug interaction (such as complexation of fluoroquinolones with multivalent cations resulting in reduced absorption) can lead to potentially subtherapeutic serum concentrations. Accelerated drug elimination is also possible. This can occur in patients with cystic fibrosis or during pregnancy, when more rapid clearance or larger volumes of distribution can 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 sites such as the CNS, eye, and prostate gland. Drug failure also can result from drugs that are highly protein bound or that are chemically inactivated at the site of infection.

Failures Caused by Host Factors

Host defenses must be considered when evaluating a patient who is not responding to antimicrobial therapy. Patients who are immunosuppressed (eg, granulocytopenia from chemotherapy or AIDS) may respond poorly to therapy because their defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens. A good example is the poor response of infection in granulocytopenic patients that is seen when their WBC counts remain low during therapy. This contrasts with a much better response when granulocyte counts increase during therapy. Other host factors are related to the need for surgical drainage of abscesses or removal of foreign bodies, necrotic tissue, or both. If these situations are not corrected, they result in persistent infection and, occasionally, bacteremia despite adequate antimicrobial therapy.

Failures Caused by Microorganisms

There are two types of resistance: intrinsic and acquired. Intrinsic is when the antimicrobial agent never had activity against the bacterial species. For example, gram-negative bacteria are naturally resistant to vancomycin because the drug cannot penetrate the outer membrane of gram-negative bacteria. Acquired resistance is when the antimicrobial agent was originally active against the bacterial species but the genetic makeup of the bacteria has changed so the drug can no longer be effective.[53] The strategies used by bacteria to develop acquired resistance are primarily classified into three general mechanisms of resistance: (a) alteration in the target site, (b) changes in membrane permeability (eg, upregulation of efflux pumps, porin channel alterations), and (c) enzymatic inactivation. Bacteria can use one or more of these mechanisms against a specific antibiotic or antibiotic class. Furthermore, a single mechanism of resistance can result in resistance to multiple related or unrelated classes of antibiotics.

Enzymatic inactivation through production of β-lactamases can be either plasmid or chromosomally mediated. In addition, the expression of β-lactamases can be induced or constitutive. There are now multiple types and classes of β-lactamases identified, which is beyond the scope of this chapter. However, there are several outstanding publications discussing all of the different types of β-lactamases.[4,54-56] The increase in resistance among bacteria is believed to be a result of 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. These resistance patterns are regionally variable, and susceptibility patterns in the community (or hospital) should be monitored closely to promote judicious antimicrobial selection.[57]

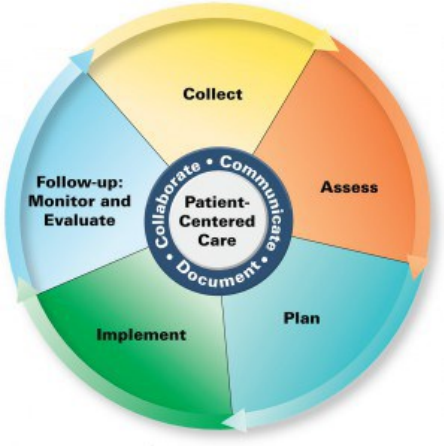
Enterococci have been isolated with multiple resistance patterns and may be resistant to β-lactams (by virtue of β-lactamase production, altered penicillin-binding proteins, or both), vancomycin (via alterations in peptidoglycan synthesis), and aminoglycosides (via enzymatic degradation). *Streptococcus pneumoniae* tends to be highly susceptible to penicillin, vancomycin, levofloxacin, moxifloxacin, and third-generation parenteral

cephalosporins. However, resistance to penicillin, certain cephalosporins (including oral third-generation cephalosporins), and macrolides has become increasingly more common. Newer antimicrobial agents such as linezolid and ceftaroline have demonstrated increased activity against penicillin and cephalosporin-resistant *S. pneumoniae.*

Treatment of an infection caused by AmpC β-lactamase producing organisms (eg, *Enterobacter* sp., *Citrobacter* sp., *Serratia marcescens*, indole-positive Proteae, *Acinetobacter* sp., or *Pseudomonas aeruginosa*) with any penicillin, cephalosporin (with the exception of cefepime), or aztreonam is strongly discouraged. Although such therapy may produce an initial clinical response by eradicating some susceptible bacteria in the population, patients will likely experience treatment failure within a few days as the highly resistant AmpC-producing subpopulations have a selective advantage and are uninhibited by these agents. AmpC β-lactamase producing organisms usually retain susceptibility to cefepime and carbapenems but are resistant to all other β-lactams. Non-β-lactam therapy, including trimethoprim/sulfamethoxazole, aminoglycosides, and fluoroquinolones are additional agents that may be utilized once susceptibilities are known. Host defenses are extremely important in this scenario and debilitated patients with pulmonary infections, abscesses, or osteomyelitis are at high risk for drug failure. In these situations, a combination regimen to prevent the emergence of resistance or the use of carbapenem may be warranted for empirical therapy.

ANTIMICROBIAL STEWARDSHIP

Patient Care Process for Infectious Diseases



Collect

- Patient presenting features (eg, age, allergies, predisposing factors)
- Patient medication history (including timing and duration of previous antibiotic use)
- Patient medical history (including past infection and culture data)
- Patient social history (eg, ethanol or illicit drug use)
- Objective data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature, height, weight
    - Labs including complete blood count (CBC) with differential and serum creatinine (SCr)
    - Cultures with susceptibilities from appropriate sites for which infectious process is a concern
    - Objective confirmation of presence of infection

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, HR >90 bpm, O_2 saturation <90% [0.9], Respiratory rate > 20 or $PaCO_2$ <32 mm Hg [4.3 kPa])

- Allergy history (including: agent(s), type of reaction, timing of reaction onset, agent(s) (if utilized) to abort reaction, etc.)
- Antimicrobial history (eg, timing, duration, and agent selection)
- Culture history (eg, prior positive cultures and susceptibilities)
- Presence of risk factors for multi-drug resistant infections (eg, recent broad-spectrum antimicrobial exposure, immunocompromising factors)
- Presence of medications with drug-drug interactions; see Table 127-2

Plan*

- Drug therapy regimen including specific antibiotic(s), dose, route, frequency, and duration
- Monitoring parameters including efficacy (eg, fever curve, complete blood count with differential) and safety (eg, nephrotoxicity, hypersensitivity reactions, CPK elevation); see Table 127-3
- Patient education (eg, purpose of therapy, medication administration, drug-drug interactions, and adverse effects); see Tables 127-2 and 127-3
- Monitoring for resolving signs and symptoms of infection and finalized culture results/susceptibilities
- Therapeutic drug monitoring based on pharmacokinetic/pharmacodynamic properties of agent (eg, AUC:MIC, Peak:MIC, trough concentrations) as appropriate
- Schedule follow-up as necessary

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up for laboratory monitoring and physical assessment as appropriate

Follow-up: Monitor and Evaluate

- Resolution of signs and symptoms of infection (eg, fever, erythema, leukocytosis, etc.)
- Presence of adverse effects (eg, nephrotoxicity, hypersensitivity reactions, CPK elevation); see Table 127-3
- Therapeutic drug monitoring based on pharmacokinetic/pharmacodynamic properties of agent (eg, AUC:MIC, Peak:MIC, trough concentrations)

**Collaborate with patient, caregivers, and other healthcare professionals.*

10 The importance of the selection and continuation of appropriate antimicrobial therapy in acute care hospitals are part of a wide movement that is referred to as “antimicrobial stewardship.” Antimicrobial stewardship programs are aimed at optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost. Many institutions have developed an antibiotic stewardship program. The team is generally a multidisciplinary group including representation from microbiology, infection control, administration, information technology, pharmacy including infectious disease-trained clinical pharmacists, and physicians from several disciplines, including infectious disease. Components of antimicrobial stewardship activities include formulary restriction, prospective audit and feedback of antimicrobial prescriptions to clinicians, education, use of clinical order sets and guidelines, de-escalation of therapy, and intravenous to oral antimicrobial conversion.[58,59]

Antibiotic Formulary

One of the main roles of an antimicrobial stewardship team is to decide which antibiotics to include on their formularies. The decision to have a formulary remains controversial; however, restricting choices does encourage familiarity with a core of antibiotics for residents and attending

physicians. Open formularies allow the empirical use of any commercially available antibiotics, with recommended guidelines for changes when culture and sensitivity results are finalized. The implementation of the guidelines and restrictions requires the cooperation of the entire medical staff. Education is vital to the success of the antibiotic formulary.

Attention must be paid to the literature on antimicrobials to assist in the selection of therapy. Evidence-based practice guidelines from the Infectious Diseases Society of America can aid clinicians to direct appropriate therapy for specific infectious disease syndromes. In addition, the results from prospective, controlled, randomized clinical trials should be evaluated whenever possible when considering appropriate antimicrobial therapy. Results from prelicensing open trials offer only limited information that can be useful in this regard because patients in these trials generally are not seriously ill and are not infected with multiple resistant bacteria. Other confounding factors found in most clinical situations are excluded by virtue of the study design. Therefore, comparative data in more seriously ill patients are essential for the appropriate application of new agents.

Post-marketing trials are also important because results can demonstrate superiority of one regimen over another, as it relates to efficacy, safety, or cost-effectiveness. Appropriate antimicrobial therapy can change as new organisms are discovered, susceptibility patterns change, new drugs become available, and new clinical trial results are published. Classical thinking in the treatment of infectious diseases will continue to change and evolve to maintain antimicrobial efficacy. Optimal use of modern antimicrobials is just beginning to be defined.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AST	antimicrobial susceptibility testing
AUC	area under the curve
CSF	cerebrospinal fluid
ESBL	extended-spectrum β-lactamase
HA-MRSA	hospital-acquired methicillin-resistant *Staphylococcus aureus*
IL-1	interleukin 1
MIC	minimal inhibitory concentration
PBP	penicillin-binding protein
PMN	polymorphonuclear
WBC	white blood cell

REFERENCES

1. Suda KJ, Hicks LA, Roberts RM, et al. Antibiotic expenditures by medication, class, and healthcare setting in the United States, 2010-2015. *Clin Infect Dis.* 2018;66(2):185–190. 10.1093/cid/cix773.

2. Centers for Disease Control and Prevention (CDC) Improve Antibiotic Use Initiative 2020 [updated 2020-11-05]. Available from: https://www.cdc.gov/sixeighteen/hai/index.htm#anchor_1603387115.

3. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America Guidance on the treatment of extended-spectrum β-lactamase producing enterobacterales (ESBL-E), carbapenem-resistant enterobacterales (CRE), and pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). *Clin Infect Dis.* 2021;72(7):e169–e183. 10.1093/cid/ciaa1478.

4. Bennett J, Dolin R, Blaser M. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 9th ed. Philadelphia, PA: Elsevier Health Sciences; 2020.

5. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200(7):e45–e67. doi: 10.1164/rccm.201908-1581ST.

6. van Ettekoven CN, van de Beek D, Brouwer MC. Update on community-acquired bacterial meningitis: Guidance and challenges. *Clin Microbiol Infect.* 2017;23(9):601–606. 10.1016/j.cmi.2017.04.019.

7. McGill F, Heyderman RS, Panagiotou S, et al. Acute bacterial meningitis in adults. *Lancet.* 2016;388(10063):3036–3047. 10.1016/s0140-6736(16)30654-7.

8. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. *Clin Infect Dis.* 2015;61(6):e26–e46. doi: 10.1093/cid/civ482.

9. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis.* 2011;52(3):e18–e55. 10.1093/cid/ciq146.

10. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435–1486. 10.1161/cir.0000000000000296.

11. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis.* 2017;64(6):e34–e65. doi: 10.1093/cid/ciw861.

12. Timbrook TT, Morton JB, McConeghy KW, et al. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: A systematic review and meta-analysis. *Clin Infect Dis.* 2017;64(1):15–23. 10.1093/cid/ciw649.

13. Messacar K, Hurst AL, Child J, et al. Clinical impact and provider acceptability of real-time antimicrobial stewardship decision support for rapid diagnostics in children with positive blood culture results. *J Pediatric Infect Dis Soc.* 2017;6(3):267–274. 10.1093/jpids/piw047.

14. Pardo J, Klinker KP, Borgert SJ, et al. Clinical and economic impact of antimicrobial stewardship interventions with the FilmArray blood culture identification panel. *Diagn Microbiol Infect Dis.* 2016;84(2):159–64. doi: 10.1016/j.diagmicrobio.2015.10.023.

15. MacVane SH, Nolte FS. Benefits of adding a rapid PCR-based blood culture identification panel to an established antimicrobial stewardship program. *J Clin Microbiol.* 2016;54(10):2455–2463. 10.1128/jcm.00996-16.

16. Mahrous AJ, Thabit AK, Elarabi S, et al. Clinical impact of pharmacist-directed antimicrobial stewardship guidance following blood culture rapid diagnostic testing. *J Hosp Infect.* 2020;106(3):436–446. doi: 10.1016/j.jhin.2020.09.010.

17. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2019;68(10):1611–1615. doi: 10.1093/cid/ciz021.

18. McPherson R, Pincus M. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 23rd ed. Philadelphia, PA: Elsevier Health Sciences; 2017.

19. Shenoy ES, Macy E, Rowe T, et al. Evaluation and mamgement of penicillin allergy: A review. *Jama.* 2019;321(2):188–199. doi: 10.1001/jama.2018.19283.

20. Vorobeichik L, Weber EA, Tarshis J. Misconceptions surrounding penicillin allergy: Implications for anesthesiologists. *Anesth Analg.* 2018;127(3):642–649. doi: 10.1213/ane.0000000000003419.

21. Sacco KA, Bates A, Brigham TJ, et al. Clinical outcomes following inpatient penicillin allergy testing: A systematic review and meta-analysis. *Allergy*. 2017;72(9):1288–1296. 10.1111/all.13168.

22. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;53(7):e25–76. 10.1093/cid/cir531.

23. Hommos MS, Glassock RJ, Rule AD. Structural and functional changes in human kidneys with healthy aging. *J Am Soc Nephrol.* 2017;28(10):2838–2844. doi: 10.1681/asn.2017040421.

24. Muanda FT, Sheehy O, Bérard A. Use of antibiotics during pregnancy and the risk of major congenital malformations: A population based cohort study. *Br J Clin Pharmacol.* 2017;83(11):2557–2571. 10.1111/bcp.13364.

25. Tasnif Y, Morado J, Hebert MF. Pregnancy-related pharmacokinetic changes. *Clin Pharmacol Ther.* 2016;100(1):53–62. doi: 10.1002/cpt.382.

26. Briggs GGF, Roger K, Towers, Craig V, Forinash, Alicia B. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.* 11th Edition. Philadelphia, PA: Lippincott Williams & Wilkins (LWW); 2017.

27. Bookstaver PB, Bland CM, Griffin B, et al. A review of antibiotic use in pregnancy. *Pharmacotherapy*. 2015;35(11):1052–1062. 10.1002/phar.1649.

28. Devaleenal Daniel B, Ramachandran G, Swaminathan S. The challenges of pharmacokinetic variability of first-line anti-TB drugs. *Expert Rev Clin Pharmacol.* 2017;10(1):47–58. doi: 10.1080/17512433.2017.1246179.

29. Lea-Henry TN, Carland JE, Stocker SL, et al. Clinical pharmacokinetics in kidney disease: Fundamental principles. *Clin J Am Soc Nephrol.* 2018;13(7):1085–95. doi: 10.2215/cjn.00340118.

30. Lewis SJ, Mueller BA. Antibiotic dosing in patients with acute kidney injury: “Enough but not too much”. *J Intensive Care Med.* 2016;31(3):164–176. 10.1177/0885066614555490.

31. Ulldemolins M, Roberts JA, Lipman J, et al. Antibiotic dosing in multiple organ dysfunction syndrome. *Chest*. 2011;139(5):1210–1220. 10.1378/chest.10-2371.

32. Crass RL, Rodvold KA, Mueller BA, et al. Renal dosing of antibiotics: Are we jumping the gun? *Clin Infect Dis.* 2019;68(9):1596–1602. 10.1093/cid/ciy790.

33. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol.* 2018;69(2):406–460. 10.1016/j.jhep.2018.03.024.

34. Rodvold KA, Piscitelli SC, Rodvold K, et al. *Drug Interactions in Infectious Diseases*. 3rd ed. New York: Totowa, NJ: Humana Press: Imprint: Humana; 2011.

35. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52(4):e56–e93. doi: 10.1093/cid/cir073.

36. Drusano GL. Pharmacokinetics and pharmacodynamics of antimicrobials. *Clin Infect Dis.* 2007;45(Suppl 1):S89–S95. doi: 10.1086/518137.

37. Guilhaumou R, Benaboud S, Bennis Y, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation-SFAR). *Crit Care*. 2019;23(1):104. doi: 10.1186/s13054-019-2378-9.

38. Sumi CD, Heffernan AJ, Lipman J, et al. What antibiotic exposures are required to suppress the emergence of resistance for Gram-negative bacteria? A systematic review. *Clin Pharmacokinet*. 2019;58(11):1407–1443. doi: 10.1007/s40262-019-00791-z.

39. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2020;77(11):835–864. 10.1093/ajhp/zxaa036.

40. Thabit AK, Hobbs ALV, Guzman OE, et al. The pharmacodynamics of prolonged infusion β-lactams for the treatment of pseudomonas aeruginosa infections: A systematic review. *Clin Ther.* 2019;41(11):2397–2415. doi: 10.1016/j.clinthera.2019.09.010.

41. Labreche MJ, Graber CJ, Nguyen HM. Recent updates on the role of pharmacokinetics-pharmacodynamics in antimicrobial susceptibility testing as applied to clinical practice. *Clin Infect Dis.* 2015;61(9):1446–1452. 10.1093/cid/civ498.

42. Ritchie David J. Antimicrobial pharmacodynamics in theory and clinical practice: Antimicrobial pharmacodynamics in theory and clinical practice, second edition. *Clinical Infectious Diseases*. 2008;46(12):1942. doi: 10.1086/588473.

43. Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: It's not just for mice anymore. *Clin Infect Dis.* 2007;44(1):79–86. doi: 10.1086/510079.

44. Kumta N, Roberts JA, Lipman J, et al. A systematic review of studies reporting antibiotic pharmacokinetic data in the cerebrospinal fluid of critically ill patients with uninflamed meninges. *Antimicrob Agents Chemother.* 2020;65. 1 10.1128/aac.01998-20.

45. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63(5):e61–e111. 10.1093/cid/ciw353.

46. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):987–994. 10.1093/cid/ciy149.

47. Pogue JM, Kaye KS, Cohen DA, et al. Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens. *Clin Microbiol Infect.* 2015;21(4):302–312. 10.1016/j.cmi.2014.12.025.

48. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev.* 2012;25(3):450–470. 10.1128/cmr.05041-11.

49. Kengkla K, Kongpakwattana K, Saokaew S, et al. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: A systematic review and network meta-analysis. *J Antimicrob Chemother.* 2018;73(1):22–32. 10.1093/jac/dkx368.

50. Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. *Surg Infect (Larchmt).* 2017;18(1):1–76. 10.1089/sur.2016.261.

51. Paul M, Lador A, Grozinsky-Glasberg S, et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database of Systematic Reviews*. 2014(1). doi: 10.1002/14651858.CD003344.pub3.

52. Roger C, Louart B, Elotmani L, et al. An international survey on aminoglycoside practices in critically ill patients: The AMINO III study. *Annals of*

Intensive Care. 2021;11. 1 10.1186/s13613-021-00834-4.

53. Partridge SR, Kwong SM, Firth N, et al. Mobile genetic elements associated with antimicrobial resistance. *Clin Microbiol Rev.* 2018;31. 4 10.1128/cmr.00088-17.

54. Ruppé É, Woerther PL, Barbier F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. *Ann Intensive Care*. 2015;5(1):61. doi: 10.1186/s13613-015-0061-0.

55. Bush K. The ABCD's of β-lactamase nomenclature. *J Infect Chemother.* 2013;19(4):549–59. doi: 10.1007/s10156-013-0640-7.

56. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother.* 2010;54(3):969–976. doi: 10.1128/aac.01009-09.

57. Strich JR, Heil EL, Masur H. Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. *J Infect Dis.* 2020;222(Suppl 2):S119–S131. 10.1093/infdis/jiaa221.

58. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis.* 2016;62(10):e51–e77. 10.1093/cid/ciw118.

59. (CDC) CfDCaP. CDC. *Core Elements of Hospital Antibiotic Stewardship Programs*. Atlanta, GA: US Department of Health and Human Services, CDC; 2019.

APPENDIX 127-1: DRUG(S) OF CHOICE, *ALTERNATIVE(S)*

GRAM-POSITIVE COCCI		
Organism	**Drug(s) of Choice**	***Alternatives***
Enterococcus faecalis Serious infections	Ampicillin, penicillin G (± gentamicin or ceftriaxone)	*Vancomycin daptomycin[a], linezolid*
Enterococcus faecalis Urinary tract infection	Ampicillin, amoxicillin	*Fosfomycin, nitrofurantoin*
Enterococcus faecium *Recommend consultation with ID specialist*	Vancomycin, linezolid, daptomycin[a]	*Eravacycline, omadacycline*
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	Nafcillin, oxacillin, cefazolin	*Daptomycin[a], trimethoprim/sulfamethoxazole, clindamycin[b], BL/BLI*
Methicillin-resistant *Staphylococcus aureus* (MRSA) Serious infections	Vancomycin, daptomycin[a]	*Linezolid, ceftaroline*
Methicillin-resistant *Staphylococcus aureus* (MRSA) SSTIs, CAP	Doxycycline, trimethoprim/sulfamethoxazole	*Clindamycin, linezolid, oritivancin, tedizolid, telavancin, dalbavancin*
Group A *Streptococcus* (*S. pyogenes*)	Penicillin G (± clindamycin *or* linezolid[c])	*Erythromycin, azithromycin, clarithromycin*
Group B *Streptococcus* (*S. agalactiae*)	Penicillin G, ampicillin, amoxicillin	*Cephalexin, clindamycin[b], vancomycin, azithromycin*
Group C, F, G *Streptococcus*	Penicillin G, penicillin V, ampicillin	*Daptomycin[a], clindamycin[b], cefazolin*
Viridans group *Streptococcus*	Penicillin G	Ceftriaxone, cefotaxime, vancomycin doxycycline
Penicillin-susceptible *Streptococcus pneumoniae*	Penicillin G, ampicillin, amoxicillin	*Ceftriaxone, doxycycline*
Penicillin-resistant *Streptococcus pneumoniae*	Ceftriaxone, vancomycin	*Levofloxacin, moxifloxacin, vancomycin, linezolid, ceftaroline*

GRAM-NEGATIVE COCCI		
Organism	**Drug(s) of Choice**	***Alternatives***
Moraxella catarrhalis	Ampicillin/sulbactam, amoxicillin/clavulanate	*Trimethoprim/sulfamethoxazole, doxycycline, azithromycin, ceftriaxone*
Neisseria gonorrhoeae	Ceftriaxone	*Gentamicin + azithromycin*
Neisseria meningitides	Penicillin G, ceftriaxone	*Moxifloxacin, ampicillin*

GRAM-POSITIVE BACILLI		
Organism	**Drug(s) of Choice**	***Alternatives***
Clostridium perfringes	Penicillin G (± clindamycin)	Metronidazole, ceftriaxone, ampicillin, piperacillin/tazobactam, meropenem, imipenem/cilastatin
Clostridioides difficile (formerly *Clostridium difficile*)	PO vancomycin, fidaxomicin	*Metronidazole*

GRAM-NEGATIVE BACILLI		
Organism	**Drug(s) of Choice**	***Alternatives***
Acinetobacter spp.	Cefepime, meropenem, imipenem/cilastatin, ampicillin/sulbactam	*amikacin, fluoroquinolone, minocycline, piperacillin/tazobactam, tigecycline, trimethoprim/sulfamethoxazole*
Bacteroides spp.	Metronidazole	*BL/BLI[f] meropenem, imipenem, cefoxitin*
Enterobacter spp.	Cefepime, meropenem, imipenem/cilastatin	*Trimethoprim/sulfamethoxazole, amikacin, piperacillin/tazobactam, fluoroquinolone[e], tigecycline*
Escherichia coli	Ceftriaxone	*Cefepime, BL/BLI, fluoroquinolone[e], trimethoprim/sulfamethoxazole, cephalexin, nitrofurantoin (cystitis), carbapenem[g]*
Haemophilus influenzae	Ampicillin/sulbactam, ceftriaxone *If* β-lactamase-negative, *may use ampicillin*	*Trimethoprim/sulfamethoxazole, azithromycin, fluoroquinolone[e], carbapenem[g]*
Klebsiella pneumoniae	Ceftriaxone, BL/BLI	*Cefepime, carbapenem[g], fluoroquinolone[e]*
Legionella spp.[d]	Levofloxacin, moxifloxacin, azithromycin	*Erythromycin, ciprofloxacin*
Pasteurella multocida	Ampicillin/sulbactam	*Penicillin G, doxycycline, trimethoprim/sulfamethoxazole*
Proteus mirabilis	Ceftriaxone	*Penicillin G, BL/BLI[f], cefepime*
Indole-positive *Proteus* (ie, *Providencia spp., Morganella morganii*)	Cefepime, meropenem, imipenem/cilastatin	*Trimethoprim/sulfamethoxazole, amikacin, piperacillin/tazobactam, fluoroquinolone[e], minocycline, tigecycline*
Pseudomonas aeruginosa	Cefepime, meropenem, amikacin, tobramycin, imipenem/cilastatin, piperacillin/tazobactam	*Ceftazidime, ciprofloxacin, levofloxacin, aztreonam*
Salmonella typhi	Ceftriaxone	*Ciprofloxacin, levofloxacin, sulfamethoxazole/trimethoprim, carbapenem[g]*
Serratia marcescens	Cefepime, meropenem, imipenem/cilastatin	*Trimethoprim/sulfamethoxazole, amikacin, piperacillin/tazobactam, fluoroquinolone[e]*
Stenotrophomonas maltophilia	Trimethoprim/sulfamethoxazole	*Minocycline, levofloxacin[h]*

MISCELLANEOUS MICROORGANISMS		
Organism	**Drug(s) of Choice**	***Alternatives***
Chlamydia pneumoniae	Azithromycin, clarithromycin, doxycycline	*Levofloxacin, moxifloxacin*
Mycoplasma pneumoniae	Azithromycin, clarithromycin, doxycycline	*Levofloxacin, moxifloxacin*
Treponema pallidum	Penicillin G	*Ceftriaxone*

MULTI-DRUG RESISTANT (MDR) GRAM-NEGATIVE ORGANISMS		
Organism	**Drug(s) of Choice**	***Alternatives***
Any ESBL-positive *Enterobacterales* Infections outside the urinary tract	Carbapenem[g]	Trimethoprim/sulfamethoxazole[i], fluoroquinolone[e, i]
Any ESBL-positive *Enterobacterales* Pyelonephritis	Trimethoprim/sulfamethoxazole	*Carbapenem[g], levofloxacin, ciprofloxacin*
Any ESBL-positive *Enterobacterales* Cystitis	Nitrofurantoin	*Trimethoprim/sulfamethoxazole, levofloxacin, ciprofloxacin*
Any *Enterobacterales* positive for KPC carbapenemase	Meropenem/vaborbactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam	*Cefiderocol*
Any *Enterobacterales* positive for ametallo-β-lactamase (ie, VIM, NDM, or IMP)	Ceftazidime/avibactam + aztreonam	*Cefiderocol*
Any *Enterobacterales* positive for OXA-48 carbapenemase	Ceftazidime/avibactam	*Cefidericol*
***Pseudomonas aeruginosa* resistant to all routinely tested β-lactams**	Ceftolozane/tazobactam	*Ceftazidime/avibactam, imipenem/cilastatin/relebactam, cefiderocol*

Above the abbreviations in the footnotes please add: "*Recommendations in chart are assuming in vitro susceptibility*"

ESBL: extended-spectrum β-lactamase; GAS: Group A *Streptococcus*; CAP: community acquired pneumonia; SSTIs: skin and soft tissue infections; BL/BLI: β-Lactam/β-lactamase inhibitor

[a]Daptomycin does not achieve appreciable CNS concentrations and therefore would not be recommended for treatment of meningitis.

[b]Clindamycin is not an appropriate alternative for treatment of bloodstream or CNS infections.

[c]Both clindamycin and linezolid provide anti-toxin activity against GAS and selection of agent dependent upon patient-specific factors.

[d]May consider the addition of rifampin for serious *Legionella* infections.

[e]Fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin.

[f]β-Lactam/β-lactamase inhibitor combination: ampicillin–sulbactam, piperacillin–tazobactam, ticarcillin–clavulanate, amoxicillin–clavulanate.

[g]Carbapenem: meropenem, imipenem/cilastatin, ertapenem.

[h]Levofloxacin should not be used as monotherapy for treatment of *Stenotrophomonas maltophilia.*

[i]Oral step-down therapy to trimethoprim/sulfamethoxazole, levofloxacin, or ciprofloxacin may be considered after (1) susceptibility to the oral agent is demonstrated, (2) patients are afebrile and hemodynamically stable, (3) appropriate source control is achieved, and (4) there are no issues with intestinal absorption.

SELF-ASSESSMENT QUESTIONS

1. Which of the following are true regarding Antimicrobial Stewardship programs?
   A. Antimicrobial stewardship programs are aimed at optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize patient outcomes.
   B. The main goal of antimicrobial stewardship programs is to minimize all costs to manage all infectious diseases.
   C. A successful antimicrobial stewardship program involves primarily the participation of the infection control department.
   D. None of the above are true.
2. Important considerations when selecting empiric antimicrobial therapy include which of the following?
   A. Prior antimicrobial use
   B. Site of infection and the organisms most likely present
   C. Prior knowledge of colonization or infections
   D. All of the above
3. Which of the following groups of physical examination findings and laboratory values is suggestive of an infection?
   A. Temperature 98.9°F (37.2 °C); WBC 11 × 10^3/mm^3 (11 × 10^9/L); Bands 0%
   B. Temperature 98.1°F (36.7 °C); WBC 6.1 × 10^3/mm^3 (6.1 × 10^9/L); Bands 2%
   C. Temperature 96.4°F (35.8 °C); WBC 21 × 10^3/mm^3 (21 × 10^9/L); Bands 10%
   D. All of the above
4. Which of the following statements considering microbiological studies in antimicrobial therapy is false:
   A. A delay in obtaining cultures until after antimicrobial therapy is started might result in false-negatives.
   B. Ideally two sets of blood cultures should be obtained peripherally from two different sites 1 hour apart.
   C. Coagulase-negative staphylococci recovered from blood cultures always warrant antimicrobial treatment.
   D. Urine cultures should be evaluated in conjunction with results of the urinalysis to confirm infection.

5. Change from parenteral to oral therapy may be considered based on which of the following factor(s)?

   A. Tolerating oral diet

   B. Hemodynamically stable

   C. Afebrile for 24 hours

   D. All of the above

6. Which of the following is a major antibiotic-drug interaction?

   A. Rifampin–Warfarin

   B. Erythromcyin–Amiodarone

   C. Isoniazid–Phenytoin

   D. All of the above

7. Which of the following is not an antimicrobial pharmacodynamic parameter?

   A. AUC:MIC

   B. *% T* above MIC

   C. MIC:bioavailability

   D. Peak:MIC

8. Which of the following statements regarding synergy and combination antimicrobial therapy is true:

   A. The combination of any two antimicrobials will always result in synergistic effects

   B. There is strong evidence to support synergistic combinations for the treatment of gram-negative bacilli in all infectious diseases.

   C. An example of synergy is the addition of an aminoglycoside to a penicillin in the treatment of enterococcal endocarditis.

   D. None of the above.

9. Identify the most appropriate monitoring parameter to assess response to antimicrobial therapy.

   A. Re-culture twice daily to ensure adequate microbiological cure

   B. Complete blood cell count with differential

   C. Serum electrolytes

   D. Caloric intake

10. Which of these statements provides the best rationale for the use of combination therapy:

    A. Combination therapy broadens spectrum of coverage for empirical therapy.

    B. Combination therapy may decrease the occurrence of toxicities.

    C. Prolonged combination therapy has been consistently proven to improve outcomes in clinical trials.

    D. All of the above.

11. Which of the following group of antimicrobials is known to cause nephrotoxicity?

    A. Colistin, tobramycin, rifamycins, tetracycline

    B. Chloramphenicol, tobramycin, colistin, vancomycin

    C. Ceftriaxone, amikacin, doxycycline, linezolid

    D. Vancomycin, moxifloxacin, tobramycin, tetracycline

12. In a patient with liver insufficiency, which of the following medications would warrant dose-adjustment?

    A. Vancomycin

    B. Cefazolin

    C. Metronidazole

    D. Ciprofloxacin

13. What scenario may not be associated with poor clinical response to antimicrobial therapy?

    A. Inadequate source control

    B. Inadequate antimicrobial spectrum

    C. Antimicrobial therapy in a neutropenic patient

    D. Antimicrobial combination is not concentration dependent

14. A concern of using combination therapy would include:

    A. Increase risk for super-infections

    B. Increase risk for drug toxicities

    C. Possibility of antagonistic effects of combination of 2 or more antibiotics

    D. All of the above

15. Activities of an antimicrobial stewardship programs may include which of the following:

    A. Antimicrobial utilization reporting

    B. Providing education for the appropriate use of antimicrobials

    C. Prospective audit and feedback

    D. All of the above

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Please see the "Antimicrobial Stewardship Principles" section for more details.

2. **D.** Each of the following considerations are important when selecting empiric antimicrobial therapy. Please see Table 127-1.

3. **C.** Answer choice C represents the grouping of findings most likely suggestive of an infection with a temperature (<96.8°F) and elevated WBC count

with an increase in immature neutrophils (bands).

4. **C.** Coagulase-negative staphylococci recovered from blood cultures often represents contamination with colonizing skin flora.

5. **D.** Please see the "Monitoring Therapeutic Response" section.

6. **D.** Please see Table 127-2.

7. **C.** Although bioavailability is important when managing patients with infectious diseases, it is not a consideration when utilizing serum or plasma concentrations of drug to calculate pharmacodynamic parameters.

8. **C.** Answer choice A is incorrect as combination therapy will not always result in synergy, and in fact may at times result in antagonism. See the "Synergism" section for more detailed explanation.

9. **B.** Answer choices C and D are incorrect as caloric intake and serum electrolytes are not utilized to monitor microbiological response. Answer choice A is incorrect as a blood culture should be obtained every 48 hours until culture clearance.

10. **A.** Answer choices B and C are incorrect as combination therapy may increase occurrence of toxicity and has failed to demonstrate improved outcomes in clinical trials.

11. **B.** See Table 127-3 for more detailed information related to nephrotoxicity of antimicrobial therapy.

12. **C.** Metronidazole is the only agent which may require dose adjustment with severe hepatic impairment.

13. **D.** Patients with immunocompromising conditions, scenarios where there is inadequate source control, and antimicrobial therapy considered inadequate for present infection are all risk factors associated with poor clinical response.

14. **D.** Increased occurrence of drug toxicities, antagonistic effects of antibiotics utilized in combination, and risk of super infection are all complications associated with combination therapy.

15. **D.** Antimicrobial stewardship programs may be involved in each of the listed tasks. Please see the "Antimicrobial Stewardship Principles" section for more details.