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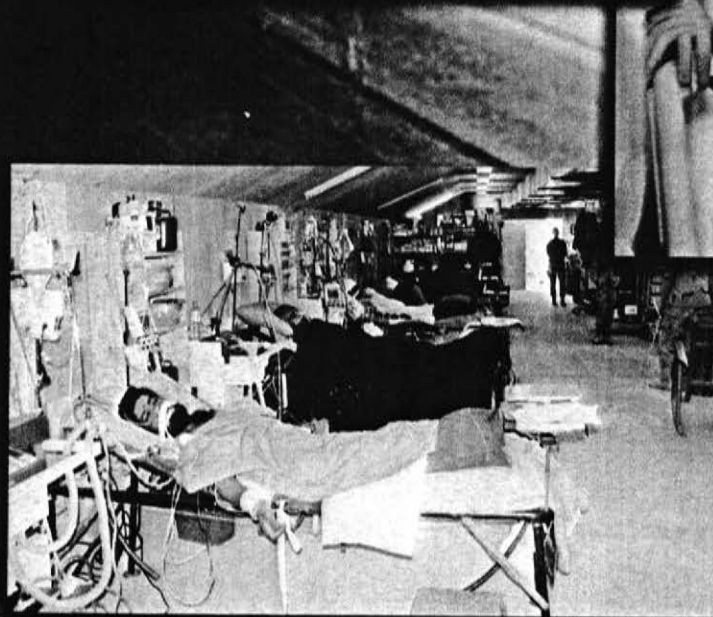
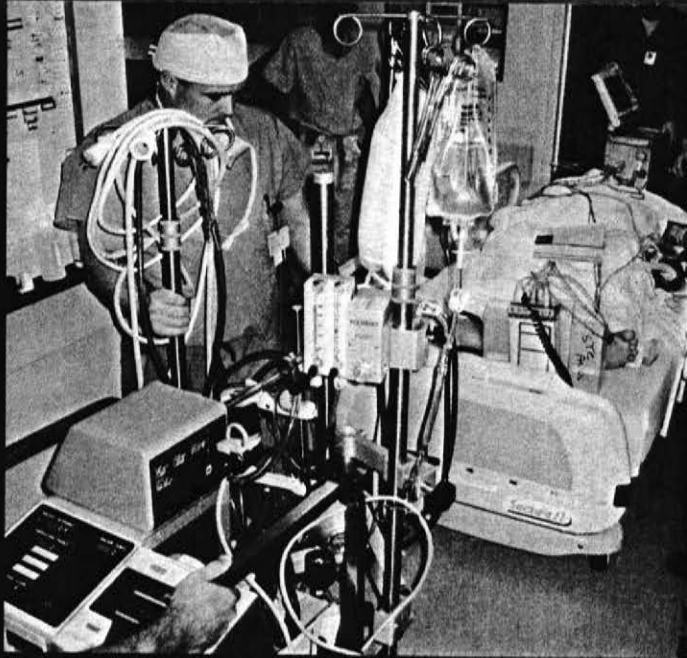


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TRAUMA

Critical Care

VOLUME 2



edited by

William C. Wilson

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Antimicrobial Therapy

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INTRODUCTION

Infections occurring in the intensive care unit (ICU) almost always involve nosocomial organisms, which are more resistant and more virulent than those typically acquired in the community. Nosocomial infections develop in approximately 24% of medical ICU patients, and 31% of surgical ICU patients (1), increasing morbidity (2), and prolonging hospital stay (3).

Trauma related injuries are the second largest source of health care costs in the United States (US) (3), and account for a significant portion of morbidity and mortality in all regions of the world (4,5). Infections in trauma patients can increase mortality up to three-fold (6).

The principles of antimicrobial use and the mechanisms of antibacterial resistance are reviewed in the first two sections of this chapter. Next, the factors increasing the risk of infectious disease following trauma and critical care are reviewed. The remainder of the chapter reviews the important clinical considerations for the various antimicrobial drugs currently in use.

All antibiotics must be evaluated in terms of their antimicrobial spectra, toxicities, and pharmacokinetic and pharmacodynamic attributes. Susceptibility results of antimicrobials reflect *in vitro* properties and do not always correlate with clinical results. Hence the reader is advised to consider many factors during antimicrobial selection (7). Several antibiotic choices are usually effective in the treatment of most infections. The recommendations listed here reflect the perspectives of two infectious diseases physicians and an infectious diseases pharmacist specialist.

PRINCIPLES OF ANTIMICROBIAL USE

Antimicrobial selection for trauma and critical care is based on the following seven considerations: (i) whether the antibiotics are planned for prophylaxis or treatment of an established infection; (ii) the anatomic site of infection; (iii) whether the infection is community-acquired or nosocomial; (iv) best guess of the most probable causative microorganism (based upon geographical and institutional isolate profiles); (v) the patient's innate immunological status; (vi) the severity of the infection and general condition of the patient; and (vii) financial cost. Ant

General Rules for Selecting Single vs. Multiple Antibiotics

On some occasions, a single antibiotic is appropriate, for example, the treatment of cellulitis with cefazolin. However, there are several circumstances where combination antimicrobial treatment should be employed. The first is the prevention of the emergence of resistant organisms while on therapy; an example is the absolute necessity to use an anti-staphylococcal agent, like nafcillin, in combination with rifampin to prevent the emergence of rifampin-resistant mutations, which are single-step mutations to full resistance in the gene that encodes the bacterial RNA polymerase, the rifampin site of action. A second example is with polymicrobial infections (e.g., intraperitoneal and pelvic infections). The flora causing these infections includes gram-negative enteric rods, a multiplicity of different obligately anaerobic species, as well as enterococci and, occasionally, yeast. A third circumstance where antimicrobial combinations is in empiric therapy where early aggressive treatment improves survival and mixed microbial infection is probable, for example, necrotizing fasciitis.

Antibiotic Synergy vs. Antagonism

In order to use combinations of antimicrobial drugs properly, the prescriber should be familiar with the concepts of antibiotic synergy and antagonism. Synergy occurs when the use of one antibiotic enhances the antimicrobial activity of another. In general, synergy occurs when the agents of any particular combination act on different biochemical pathways of the microorganism or act sequentially along the same metabolic pathway; an example of the first is the use of ampicillin (or vancomycin) and gentamicin against enterococci. Aminoglycosides are ineffective as single drugs in treating gram-positive organisms because they cannot penetrate the thick peptidoglycan cell wall to reach their site of action at the ribosome within the bacterial cytoplasm. The combination of ampicillin (or vancomycin) and gentamicin is synergistic for enterococci because ampicillin (and vancomycin) damage the bacterial cell wall (as their antimicrobial mechanism of action) thereby allowing the aminoglycoside to penetrate into the cell. Clinical studies have shown that the addition of gentamicin to ampicillin significantly improves outcome in patients with enterococcal endocarditis, even though enterococci are relatively resistant to ampicillin (8). Similar effects are noted with the combination of antistaphylococcal

penicillins (or vancomycin) combined with an aminoglycoside against *Staphylococcus aureus*, but the magnitude of the effect is less. Another clinical example of synergism involves the use of anti-pseudomonal beta-lactams such as piperacillin or ticarcillin in combination with aminoglycosides to treat serious infections with *Pseudomonas aeruginosa* (9).

The combination drug trimethoprim-sulfamethoxazole (Bactrim or Septra) is an example of synergism resulting from using two antibiotics that act sequentially in the same pathway. Sulfamethoxazole acts first and trimethoprim (TMP) second in the microbial pathway for de novo synthesis of folic acid, which is necessary for synthesizing precursors for DNA and other molecules involved in bacterial intermediary metabolism. For treating fungi, 5-FC is not used alone because of the development of rapid resistance. However, the combination of 5-FC and amphotericin is synergistic in vitro, and this combination is commonly used clinically to treat cryptococcal meningitis (10).

Antagonism occurs when the combination of antibiotics is less effective than either agent alone. For example, the use of bacteriostatic drugs such as tetracycline or chloramphenicol that inhibit protein synthesis generally decrease the effectiveness of beta-lactam drugs that act on the cell wall (11). Another example of antagonism in vitro involves the use of azoles like fluconazole in combination with amphotericin. Ergosterol, a sterol in the fungal plasma membrane, is the target site of amphotericin; azole drugs inhibit the enzyme necessary for ergosterol synthesis and decreases the amount of ergosterol present in the plasma membrane, thereby decreasing the target of action for amphotericin and making it potentially less effective.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Factors influencing the emergence of resistance in microorganisms include: (i) the indiscriminant use of broad-spectrum antibiotics in medicine, (ii) the widespread use of antibiotics in animal husbandry and fisheries, (iii) prolonged hospitalizations, (iv) the increasing numbers of immunocompromised patients, (v) international travel, and (vi) medical progress resulting in increased use of invasive procedures and devices.

Bacteria evade antimicrobial action by diverse mechanisms. These mechanisms include changes in permeability of the bacterial cell wall and plasma membrane to the antibiotic, antibiotic efflux from bacterial cells, inactivation of the antibiotic (usually enzymatically), modification or elimination of the target site(s) for the antibiotic, and the development of auxotrophs (bacterial strains with growth requirements different from those of the wild-type strains) which can bypass steps inhibited by antibiotics. Understanding the general mechanism of resistance has clinical relevance when choosing a specific antibiotic for a specific organism. For example, methicillin-resistant *S. aureus* (MRSA) is resistant to beta-lactam agents by virtue of possessing an altered penicillin-binding protein (PBP), the target of all beta-lactams. Therefore, combination products increasing the duration of beta-lactam activity with a beta-lactamase inhibitor, (e.g., piperacillin/tazobactam or ampicillin/sulbactam) will not demonstrate any activity against MRSA (12–17).

♣ **A primary tenet of antimicrobial therapy is to use the narrowest spectrum antibiotic possible, rather than a broad-spectrum agent.** ♣ Empiric treatment (prior to the final identification of specific microorganisms) is by necessity broad-spectrum, and the antibiotic selection is based upon several features. These include the location where the suspected infection developed (e.g., community vs. hospital-acquired),

the anatomic site involved (e.g., oropharynx vs. colon), suspected organisms (based on prior literature and local experiences), the local antibiotic sensitivity and resistance patterns, the current gram stain and prior culture results, patient allergies, renal/hepatic function, and other clinical factors. Emergent, empiric antimicrobial treatment is indicated in only a few situations, including, for example, suspected sepsis, bacterial meningitis, some fulminant pneumonias (i.e., *Bacillus anthracis*) and some severe soft-tissue infections (i.e., necrotizing fasciitis). There is usually adequate time for a thorough clinical evaluation of a patient in other circumstances, including the collection of adequate specimens (for gram stain and culture) prior to the institution of antibiotics. Fever alone in a clinically stable patient can result from either an infection or a myriad of other causes (e.g., major trauma, burns, surgery, hematoma in soft tissue or subarachnoid blood, etc.), and frequently does not require antimicrobial therapy. (Volume 2, Chapter 46) Hence the dictum "antibiotics are not the antipyretic of choice."

Prophylactic antibiotic use in surgery should be limited to proven indications and duration. A good example of this principle are the recently published guidelines for the appropriate use of vancomycin to reduce the emergence of vancomycin-resistant enterococci (VRE) and possible vancomycin-resistant *S. aureus* (VRSA) (16). These guidelines discourage the use of vancomycin except for limited situations, which include: (i) severe beta-lactam allergy, (ii) infections caused by gram-positive cocci that are resistant to beta-lactams, (iii) empiric use in circumstances where there is a high institutional prevalence of MRSA, (iv) life threatening infections until definitive culture results return, and (v) the oral treatment of *Clostridium difficile* colitis (only when there is a failure of metronidazole) (16).

RISK FACTORS FOR INFECTIONS IN TRAUMA AND CRITICAL CARE

Many factors increase the infection risk in trauma and critical illness. Defects in the mucosal and skin surfaces after trauma allow microbes to bypass initial defenses. Chest tubes, endotracheal tubes, catheters, and drains facilitate pathogen entry. Devitalized tissues and obstruction of drainage ports (e.g., sinusitis) increase the bacterial count, impair the normal self-cleansing of bacteria, and decrease the ability of white blood cells (WBC) to have access to bacteria—all serving to increase the risk of infection. Within a few days, patients lose the normal protective skin and gut flora and become colonized with nosocomial organisms, which subsequently cause hospital-acquired infections with microbes that are often resistant to many antibiotics.

The most basic question to be answered by the physician contemplating antibiotics in a critically ill patient is whether the patient is in fact infected. The cardinal signs and symptoms of infection (elevated WBC count, fever, hyperdynamic state), and inflammation (rubor et tumor cum calore et dolore [from Celsus]—redness and swelling with heat and pain) are also common accompaniments of acute trauma, and therefore, do not necessarily indicate an infection (18). These signs can persist for days after admission, especially with multiple fractures, burns, or diffuse soft tissue injury. Further complicating infection evaluations in this patient population are patient care devices, limited mobility, and ventilators. Another clinical conundrum is deciding whether a patient is colonized or actually infected, once organisms have been isolated. This can be especially problematic when the culture isolate was derived from suctioned sputa or previously placed drains.

Infection control measures are vitally important to mitigate the spread of resistant organisms. ⚡ **As Ignaz Phillip Semmelweis discovered 150 years ago, the most important means of preventing the transmission of microorganisms from one patient (via the doctor or nurse) to another patient is strict hand washing (and now, the use of clean disposable gloves).** ⚡

Bacterial organisms commonly responsible for infections in trauma and critically ill patients are divided into three main classes: aerobic gram positive, aerobic gram negative, and anaerobic. The common gram-positive pathogens and the currently recommended antibiotics for these organisms are listed in Table 1. The recommendations provided in this and other tables in this chapter reflect general sensitivity and resistance patterns as of the publication of this textbook, and local conditions may be different.

Organisms causing infections in trauma patients have changed over time. ⚡ **At present, the majority of infections occurring in hospitalized trauma patients are due to gram-positive organisms (19), for example, MRSA and VRE, and to a lesser extent, multi-resistant gram-negative rods (20).** ⚡ This is in sharp contrast to a few decades ago where gram-negative organisms prevailed.

Gram-negative organisms include many of the enteric bacteria and some of these are developing extended spectrum beta lactamases (ESBLs), especially the so called

“SPACE” organisms (*Serratia* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp). The common gram negative aerobic bacteria, along with the antimicrobial drugs of choice, are summarized in Table 2.

With appropriate antibiotic use, fungal infections are still rare in trauma injured patients, excluding catheter-related urinary tract infections. Judicious prophylactic antibiotic use in the trauma setting is generally accepted practice in specific situations (21–24).

⚡ **Penetrating intra-abdominal injury, perforated abdominal viscera, and open fractures all warrant antibiotic prophylaxis (22–25).** ⚡

Infections involving the mouth and gastrointestinal tract (including most intraabdominal abscesses) involve anaerobic bacteria, in addition to aerobic gram-positive and gram-negative organisms. The common anaerobic pathogens involved in trauma and critical care are summarized in Table 3. In general, infections involving anaerobic organisms that occur above the diaphragm, or in the vagina, can be treated with clindamycin or metronidazole. However, those occurring from organisms native to the colon (e.g., *Bacteroides fragilis*) are best treated by metronidazole.

A complete survey of infectious and non-infectious sources of fever is provided in Volume 2, Chapter 46. Sepsis and SIRS are reviewed in great detail in Volume 2, Chapters 47 and 63, respectively. The most common

Table 1 Antimicrobial Drugs of Choice Against Aerobic Gram-Positive Bacteria

Microorganisms	Drug of choice	Alternative agents
<i>Staphylococcus aureus</i>		
Non-penicillinase-producing	Penicillin	Vancomycin, cephalosporin
Penicillinase producing	Nafcillin, oxacillin	Vancomycin, cephalosporin, erythromycin, clindamycin
MRSA	Vancomycin ^a	Linezolid, quinupristin/dalfopristin, tigecycline
VISA	Daptomycin ^b	Quinupristin/dalfopristin, linezolid
VRSA	Daptomycin ^b	Quinupristin/dalfopristin, linezolid
Alpha-streptococci (<i>Streptococcus viridans</i>)	Penicillin	Cephalosporin
Beta-streptococci (A, B, C, G)	Penicillin	Cephalosporin, erythromycin
<i>Streptococcus bovis</i>	Penicillin	Vancomycin, cephalosporin
<i>Streptococcus pneumoniae</i> (pneumococcus)		
PCN-susceptible (MIC <0.1 mcg/mL)	Penicillin or amoxicillin	Cephalosporin, erythromycin, azithromycin, clarithromycin, levofloxacin, moxifloxacin, carbapenems, clindamycin, tetracycline
PCN-intermediate resistance (MIC = 0.1–2 mcg/mL)	Penicillin or ceftriaxone, cefotaxime	Levofloxacin, gatifloxacin, moxifloxacin, clindamycin, vancomycin
PCN-high-level resistance (MIC >2 mcg/mL)	Meningitis: vancomycin + ceftriaxone or cefotaxime other indications: vancomycin + ceftriaxone or cefotaxime, linezolid, levofloxacin, gatifloxacin, moxifloxacin	Carbapenems, quinupristin/dalfopristin
<i>Enterococcus</i> spp.		
Serious infection	Ampicillin + gentamicin or streptomycin	Vancomycin + gentamicin or streptomycin; linezolid; quinupristin/dalfopristin
Uncomplicated UTI	Ampicillin	Nitrofurantoin; ciprofloxacin, levofloxacin; fosfomycin
VRE	Linezolid	Daptomycin; quinupristin/dalfopristin

^aSome studies show that linezolid was superior to vancomycin for ventilator associated pneumonia due to MRSA. However, the doses of vancomycin in these studies were subtherapeutic.

^bDaptomycin contraindicated in pneumonia (surfactant inhibits daptomycin). For pneumonia, due to VISA, or VRSA use quinupristin/dalfopristin, or linezolid. Abbreviations: MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; PCN, penicillin; UTI, urinary tract infection; VISA, vancomycin intermediate sensitive *S. aureus*; VRE, vancomycin-resistant enterococcus; VRSA, vancomycin-resistant *S. aureus*.

Table 2 Antimicrobial Drugs of Choice Against Aerobic Gram-Negative Bacteria

Microorganisms	Drug of choice	Alternative agents
<i>Acinetobacter</i> spp.	Imipenem, meropenem	Aminoglycoside, ciprofloxacin, cotrimoxazole, ceftazidime
<i>Aeromonas</i>	Cotrimoxazole	Aminoglycoside, imipenem, fluoroquinolone
<i>Enterobacter</i> spp.	Imipenem, meropenem	Aminoglycoside, ciprofloxacin, cotrimoxazole, cefepime
<i>Escherichia coli</i>	Ceftriaxone, cefotaxime	Aminoglycoside, imipenem, meropenem, ceftazidime, cefepime, cotrimoxazole, fluoroquinolone, aztreonam, piperacillin/tazobactam
<i>Haemophilus influenzae</i>	Second- or third-generation cephalosporin	Fluoroquinolone, cotrimoxazole
<i>Klebsiella pneumoniae</i>	Ceftriaxone, cefotaxime	Aminoglycoside, carbapenems, ceftazidime, aztreonam, cefepime, cotrimoxazole, fluoroquinolone, piperacillin/tazobactam
<i>Legionella</i> spp.	Azithromycin or a fluoroquinolone ± rifampin	Doxycycline ± rifampin, cotrimoxazole, erythromycin
<i>Proteus mirabilis</i>	Ampicillin	Cephalosporin, cotrimoxazole, aminoglycosides, carbapenem, fluoroquinolone, aztreonam
Other <i>Proteus</i> spp.	Ceftriaxone, cefotaxime, ceftazidime, cefepime	Imipenem, meropenem, fluoroquinolones, piperacillin/tazobactam, cotrimoxazole, aminoglycoside
<i>P. aeruginosa</i>	Ceftazidime + an aminoglycoside or cipro	Carbapenems, cefepime, aztreonam, levoflox, piperacillin
<i>Salmonella</i> spp.	Fluoroquinolone or ceftriaxone	Cotrimoxazole
<i>Stenotrophomonas maltophilia</i>	Cotrimoxazole	Fluoroquinolone
<i>Serratia</i> spp.	Carbapenem	Aminoglycoside, aztreonam, third- or fourth-generation cephalosporin, cotrimoxazole, piperacillin/tazobactam, fluoroquinolone

sources of infection in trauma and critical care also have specific chapters dedicated to them, including ventilator associated pneumonia (Volume 2, Chapter 48), indwelling catheter related infections (Volume 2, Chapter 49), abdominal sources of infection (Volume 2, Chapter 50), and sinusitis (Volume 2, Chapter 51). The remainder of this chapter reviews the antimicrobials most frequently used for trauma and critical care.

PENICILLINS

History/Description

Dr. Alexander Fleming discovered penicillin in 1929, while working on unrelated influenza research. Fleming happened upon his discovery when he observed that one of his staphylococcal culture plates became contaminated with

a mould, and that surrounding the fungi was a ring-like bacteria-free zone. Fleming subsequently diluted the mould more than 800 times, and still it retained the antibacterial effect. With the assistance of a mycologist colleague, the mould was identified as a *Penicillium*, and Fleming subsequently named the antibacterial active substance penicillin. His publication in 1929 describing this research received little attention until World War II, when penicillin use became widespread. In 1945, Fleming received the Nobel Prize for his discovery. Since that time, penicillin and its derivatives have remained the drug of choice for many bacterial infections, and modifications of its chemical structure has led to the development of numerous other beta-lactam derived antimicrobials (26–28).

Table 3 Antimicrobial Drugs of Choice Against Anaerobic Bacteria

Microorganisms	Drug of choice	Alternative agents
<i>Prevotella melanogenica</i>	Penicillin G; or clindamycin	Metronidazole
<i>Bacteroides fragilis</i>	Metronidazole	Carbapenems, cefoxitin, ampicillin/sulbactam, piperacillin/tazobactam
<i>Clostridium perfringens</i>	Penicillin or clindamycin	Metronidazole, carbapenems, chloramphenicol
<i>Clostridium tetani</i>	Metronidazole	Penicillin, a tetracycline
<i>Clostridium difficile</i>	Metronidazole	Vancomycin (oral)

Mechanism of Action, Pharmacology, Administration, and Dosage

Penicillin and other beta-lactam related antibiotics (e.g., cephalosporins, monobactams, and carbapenems) all have similar mechanisms of action, primarily targeting the peptidoglycan cell wall; these actions are characterized by enzymatic inhibition of cell wall synthesis and turnover with the resultant destruction of bacteria through autolytic enzymes. For the available penicillin agents, modifications of the side-chain results in a wide variety of pharmacokinetic properties and antimicrobial activities (Table 4).

Most penicillin antibiotics are widely distributed however, penetration across the blood-brain barrier and into the cerebrospinal fluid (CSF) and into the vitreous humor is poor, and levels are significantly lower than serum concentrations, except in the presence of inflammation. Therefore, relatively high doses of penicillins are required to treat infections in these "protected" sites.

Table 4 The Penicillins: Selected Dosing and Need for Adjustment Based Upon Renal or Hepatic Dysfunction

Penicillin sub-type	Typical adult IV dose range and intervals	Requires dose adjustment for renal insufficiency (CrCl <30 mL/min)	Requires dose adjustment for hepatic failure
Aqueous crystalline penicillin G	1–4 million units every 4–6 hr	Yes	No
Ampicillin	1–2 g every 4–6 hr	Yes	No
Ampicillin/sulbactam	1.5–3 g every 6–8 hr	Yes	No
Piperacillin	3–5 g every 4–8 hr	Yes	No
Piperacillin/tazobactam	3.375–4.5 g every 4–6 hr	Yes	No
Oxacillin	1–2 g every 4–6 hr	Yes	No
Nafcillin	1–2 g every 4–6 hr	Yes	No

Abbreviation: IV, intravenously.

Antimicrobial Activity/Spectrum/Resistance

Differential bacterial cell wall permeability, binding site affinity and susceptibility to bacterial enzymes (e.g., beta-lactamases) account for the various susceptibility patterns among different penicillins, and other beta-lactams (Tables 1–3). Bacterial production of beta-lactamases, which enzymatically destroy beta-lactam antibiotics, represent the most common mechanism of antimicrobial resistance. Gram-positive organisms usually secrete beta-lactamases extracellularly, whereas gram-negative organisms secrete small quantities of beta-lactamases within the periplasmic space. There are several types of beta-lactamases, each with various binding affinities to enzymes required for the reproduction of specific microorganisms. With this in mind, the development of beta-lactamase inhibitors, in combination with specific penicillins, provides the rationale for the clinical use of combinations (i.e., ticarcillin-clavulanate, piperacillin-tazobactam, and ampicillin-sulbactam).

Narrow-spectrum penicillins, such as penicillin G or ampicillin, remain the drug of choice for most streptococci, enterococci, and oral anaerobic bacteria. The semi-synthetic penicillins, such as nafcillin or oxacillin, were designed specifically for *S. aureus* and have neither anaerobic nor enterococcal activity, and have reduced streptococcal activity. They also lack activity against gram-negative rods. Extended spectrum penicillins, (e.g., piperacillin, mezlocillin, and ticarcillin) have improved activity against not only *P. aeruginosa* but also against additional community and hospital-acquired gram-negative rods. ⚡ **The addition of a beta-lactamase inhibitor to beta-lactam antibiotics produces efficacy against beta-lactamase-producing organisms such as *S. aureus*, *Escherichia coli*, and most anaerobic bacteria. However, these combination products add no additional activity against *P. aeruginosa* and have no activity against MRSA. ⚡ MRSA specifically lack the binding proteins for these beta lactams, and are intrinsically resistant regardless of the concentration or duration of high drug levels of beta lactams.**

Adverse Effects and Drug Interactions

Hypersensitivity reactions are the most common adverse effects encountered with the use of penicillins. These reactions range from minor, such as rash, to potentially life-threatening such as anaphylaxis (Volume 1, Chapter 33). A few unique adverse effects are seen with specific penicillins, such as platelet dysfunction with piperacillin and a

high incidence of rash with ampicillin and amoxicillin. The management of adverse effects and allergy testing is discussed below (Beta-Lactam Allergy). No clinically important drug interactions occur with the penicillins.

Therapeutic/Clinical Uses

Because of their long history of clinical safety, efficacy, and availability, the penicillins are frequently used in the critically ill patient. As seen in Table 1–3, the penicillins are the drugs of choice for many infections commonly encountered in these patients.

CEPHALOSPORINS

History/Description

Cephalosporins are a group of natural and semi-synthetic compounds that are structurally similar to penicillins and have been in clinical use since the 1960s. The cephalosporins are categorized into first-to-fourth “generation,” based upon antimicrobial spectrum. Table 5 lists the four generations of cephalosporins (29–32).

Mechanism of Action, Pharmacology Administration, and Dosage

Cephalosporins, like penicillins, enzymatically inhibit bacterial cell wall synthesis. Therapeutic cephalosporin concentrations are reached in many body sites; however, cefazolin and cephalothin do not provide adequate enough concentrations in the CSF to treat bacterial meningitis. However, several of the third and fourth generation cephalosporins reach sufficient concentrations in the CSF for therapeutic utility. These include ceftriaxone, cefotaxime, ceftizoxime, ceftazidime, and cefepime. Table 5 delineates the dosing considerations for the most commonly used cephalosporins. Uniquely, among the cephalosporins, ceftriaxone has the longest half-life and may be dosed on a once-daily basis in most clinical circumstances.

Antimicrobial Activity/Spectrum/Resistance

⚡ **In general, as one selects a second, third, or fourth generation cephalosporin, there is increased activity against aerobic gram-negative bacteria and less activity against gram-positive organisms.** ⚡ Although ceftriaxone, ceftizoxime, and cefotaxime retain excellent gram-positive activity, the cephalosporins, as a class, do not have activity against

Table 5 The Cephalosporins: Selected Dosing and Need for Adjustment Based Upon Renal or Hepatic Dysfunction

Cephalosporin generation and sub-type	Typical adult IV dose range and intervals	Requires dose adjustment for renal insufficiency (CrCl < 30 mL/min)	Requires dose adjustment for hepatic failure
First generation			
Cephalothin	1–2 g every 4–6 hr	Yes	No
Cefazolin	1–2 g every 8 hr	Yes	No
Second generation			
Cefoxitin	1–2 g every 6 hr	Yes	No
Cefuroxime	0.75–1.5 g every 8–12 hr	Yes	No
Third generation			
Cefoperazone	1–2 g every 12 hr	Yes	No
Cefotaxime	1–2 g every 4–8 hr	Yes	No
Ceftriaxone	1–2 g every 12–24 hr	Yes	No
Ceftazidime	1–2 g every 8 hr	Yes	No
Fourth generation			
Cefepime	1–2 g every 12 hr	Yes	No

Abbreviation: IV, intravenously.

enterococci, MRSA, or *Listeria monocytogenes*. For activity against *P. aeruginosa*, the use of ceftazidime or cefepime is usually required. Because of their broad activity against most aerobic gram-positive cocci (except enterococci), and gram-negative bacilli (except *P. aeruginosa*), the third generation cephalosporins (ceftriaxone, cefotaxime and ceftizoxime) are commonly used in the critically ill patient.

The first generation cephalosporins, such as cefazolin, have a wide-range of activity against almost all aerobic cocci, including MSSA (but not enterococci or MRSA) and some gram-negative bacilli (with the exception of *P. aeruginosa* and some other gram-negative rods).

☞ **The cephamycins, specifically cefoxitin and cefotetan, have unique broad-spectrum activity against most anaerobic organisms. However, there are increasing resistant forms of *B. fragilis*.** ☞ *B. fragilis* resistance has risen to such a degree that both the Infectious Disease Society of America and the Surgical Infection Society now recommend against these drugs as single agents for intra-abdominal infections (23,24,33).

Adverse Effects and Drug Interactions

The adverse effects of the cephalosporins are similar to those of the penicillins. Additionally, certain drug–drug interactions occur with cephalosporins and cephamycins, which have a methyl-thio-tetrazole side chain (cefotetan, cefoperazone, cefamandole, and moxalactam). This class of cephalosporins can produce a disulfiram-like reaction when administered with alcohol. In addition, these antibiotics can prolong the INR via inhibition of vitamin K metabolism.

Therapeutic/Clinical Uses

The third generation cephalosporins (ceftriaxone, cefotaxime, and ceftizoxime) have broad activity against most aerobic gram-positive cocci and gram-negative bacilli, (except *P. aeruginosa*), and are very commonly used for empiric therapy for Ventilator-associated pneumonia (VAP) in critical care units. Ceftazidime also has excellent activity against *P. aeruginosa* but only marginal activity against gram-positive cocci.

Advantages of the cephalosporins include their relatively low toxicity, especially compared to the aminoglycosides, their activity against certain hospital-acquired, multi-drug resistant bacteria, and the opportunity to administer a single agent rather than multiple antibiotics. Cephalosporins are not superior to the older, narrow-spectrum, and less-expensive antimicrobials. Thus, extended-spectrum cephalosporins are rarely the drug of choice for any infection. In addition, the emergence of resistance during therapy with these newer cephalosporins has been shown, including VRE, MRSA, and *C. difficile* through selection pressures.

OTHER BETA-LACTAM ANTIBIOTICS AND ADVERSE REACTIONS

Monobactams

Aztreonam is a synthetic monocyclic B-lactam (monobactam) antibiotic, and was the first approved for clinical use in the US (34,35). Monobactams differ structurally from penicillins and cephalosporins because of their monocyclic rather than a bicyclic nucleus; this novel structure explains why aztreonam has little cross-allergenicity with the bicyclic B-lactams. Although skin rashes have occurred occasionally with the use of aztreonam, the drug has been given safely to patients with immediate-type hypersensitivity reactions (e.g., anaphylaxis and urticaria) to both penicillins and cephalosporins (36). Other adverse effects are similar to those of other B-lactam drugs.

☞ **Aztreonam is devoid of antibacterial activity against gram-positive and anaerobic bacteria.** ☞ Aztreonam is clinically effective against most facultative aerobic Gram-negative bacilli. The spectrum and potency of aztreonam is similar to the third generation cephalosporin ceftazidime (37) as both contain the same 2-aminothiazolyl with a propyl-carboxy addition to its side-chain (38). Aztreonam adequately crosses the blood brain barrier and is highly active against *Haemophilus influenzae* and *N. gonorrhoeae* (including beta-lactamase-producing strains), and against most of the Enterobacteriaceae (including *E. coli*, *Klebsiella*,

Table 6 Monobactams and Carbapenems (Beta Lactam-like Drugs): Selected Dosing and Need for Adjustment Based Upon Renal or Hepatic Dysfunction

Beta lactam-like drug classification and name	Typical adult IV dose range and intervals	Requires dose adjustment for renal insufficiency (CrCl <30 mL/min)	Requires dose adjustment for hepatic failure
Monobactams			
Aztreonam	1–2 g every 8 hr	Yes	No
Carbapenems			
Imipenem/cilastatin	0.5–1.0 g every 6–8 hr	Yes	No
Meropenem	0.5–1.0 g every 6–8 hr	Yes	No
Ertapenem	1 g every 24 hr	Yes	No

Abbreviation: IV, intravenously.

Proteus, *Serratia*, *Shigella*, and *Salmonella* species). Aztreonam is slightly less potent than imipenem or ceftazidime against *P. aeruginosa*. The usual dosage of aztreonam is 1 to 2 g intravenously given every eight hours. Refer to Table 6 for selected dosing and route of administration.

Carbapenems

Carbapenems are a class of antimicrobials created by a simple substitution of a sulfur atom for a carbon atom of the beta-lactam nucleus, and the addition of a double bond to the 5-member ring comprising the penicillin nucleus (7). The first clinically available carbapenem for use in the United States was imipenem, released in 1985 followed a decade later by meropenem (released in 1996) and shortly thereafter ertapenem. Imipenem is marketed as a combination drug with cilastatin (which inhibits the renal hydrolysis of imipenem). Meropenem and ertapenem, the other currently available carbapenems, are not combined with cilastatin.

♣ **Carbapenems are the class of antibiotics with the greatest activity spectrum of any class of antibiotics for systemic use in humans. They are active against gram-positive (except MRSA), gram-negative, and anaerobic bacteria. These agents (except ertapenem) are particularly useful for hospital-acquired infections where bacterial resistance (other than MRSA and VRE) may be a concern.** ♣

Similar to the beta-lactam agents (especially the cephalosporins) the carbapenems have no activity against MRSA, *Enterococcus faecium*, and *Legionella* spp. In addition, the carbapenems have no activity against *Stenotrophomonas* (formerly *Pseudomonas maltophilia*). The activity of ertapenem does not include *P. aeruginosa* or *Acinetobacter* spp., two organisms commonly involved in hospital-acquired infections. The carbapenems, imipenem and meropenem, are considered the drugs of choice for extended-spectrum beta-lactamase (ESBL) producing organisms.

The mechanism of action is similar to that of other beta-lactam antibiotics and the toxicities are similar. In addition, imipenem is associated with an increased risk of seizures when administered in large doses to patients with renal insufficiency, a side effect caused by the cilastatin component (which decreases the seizure threshold). Refer to Table 6 for selected dosing, route of administration, and need for dose adjustment for the carbapenems. The pharmacology of meropenem has recently been reviewed (7,39).

Beta-Lactam Allergy

Beta-lactam antibiotics are the most common class of antibiotics associated with adverse reactions partly because they are the most frequently used class of antibiotics. It was previously estimated that 1% to 10% of patients receiving penicillins will develop an adverse effect (40). However, that estimate was probably high, and the incidence of potentially life-threatening anaphylactic reactions is far lower (41).

Beta-lactam allergies are classified as immediate, accelerated, or delayed. Immediate reactions are of rapid onset occurring usually <30 minutes after administration, with the clinical manifestations of laryngeal edema, bronchospasm, hypotension, urticaria (hives), pruritus, and occasionally, anaphylactic shock. These reactions are IgE-mediated (Volume 1, Chapter 33).

Accelerated reactions occur from 1 to 72 hours after antibiotic administration, with the clinical manifestations of urticaria and angioedema. Delayed reactions are those occurring 3 days to several weeks after exposure, with rash being the most common, but they may also include serum sickness, hemolytic anemia, interstitial nephritis, arthralgias, and urticaria. Only the immediate and accelerated reactions have major clinical significance in terms of antibiotic selection.

Patients with a history of an immediate or accelerated reaction to penicillins manifesting as laryngeal edema, hypotension, urticaria, and/or angioedema, should not receive penicillins or any other beta-lactam antibiotics. In the event that a patient must be given penicillin, a penicillin skin test should be performed for patients with accelerated reactions, and if positive, then desensitization is required. If negative, these agents may be given cautiously. ♣ **Patients with a history of penicillin allergy due to rash or pruritus only occurring more than 3 days after administration are no more likely to have any allergic reaction to a cephalosporin than patients without a history of penicillin allergy and can safely receive cephalosporins.** ♣

Recent studies indicate that the incidence of cross-reactivity to cephalosporins in penicillin-allergic patients is probably not more than two percent (42). Cross-reactions between penicillins and carbapenems occur much more frequently. ♣ **There is up to a 50% chance of developing a rash to carbapenems in patients with a history of rash to penicillins.** ♣ Aztreonam, a monobactam, does not appear to have any cross-reactivity in patients with immediate reactions to beta-lactams and is a useful therapeutic option when an antibiotic possessing excellent gram-negative rod activity is indicated in a beta-lactam allergic patient. ♣ **Aztreonam is**

considered a safe alternative in patients allergic to penicillins or cephalosporins requiring gram-negative coverage, and vancomycin is the recommended choice when these patients require gram-positive coverage. ⚡

AMINOGLYCOSIDES

History/Description

Aminoglycosides are naturally occurring antibacterial compounds produced by members of the Actinomycetes family that are filamentous bacteria that resemble fungi. Streptomycin (derived from *Streptomyces griseus*) was discovered in 1943, followed in 1963 by gentamicin (derived from *Actinomycetes* spp.), and tobramycin (derived from *Streptomyces tenebrarius*). The use of aminoglycosides has declined in recent years due to nephrotoxicity and the development of less toxic alternatives. However, the ability to dose these medications once daily and the relatively low level of resistance keeps the aminoglycosides in the clinical arena as a useful class of antibiotics (43,44).

Mechanism of Action, Pharmacology, Administration, and Dosage

Aminoglycosides bind to the 30S ribosomal subunit of bacteria, thereby inhibiting protein synthesis. The ability of aminoglycosides to reach ribosomes, which are intracellular, is facilitated by the concurrent use of antibiotics that inhibit the synthesis of the bacterial cell wall, such as the beta-lactam antibiotics and vancomycin. This synergistic activity accounts for the clinical use of combination of an aminoglycoside with a penicillin beta-lactam or vancomycin for serious enterococcal infections.

The aminoglycosides exert concentration-dependent killing. They also have a prolonged post-antibiotic effect that allows for once-daily dosing in many patients. Aminoglycosides have poor oral absorption and therefore are administered parenterally. Changes in the extracellular fluid compartment, as in congestive heart failure, ascites, or dehydration, will alter the volume of distribution and necessitate dosage modifications. Aminoglycosides have negligible protein binding. The average half-life for aminoglycosides in patients with normal renal function is approximately two hours. Aminoglycosides are significantly removed by hemodialysis but to a much lesser extent via peritoneal dialysis. Aminoglycosides do not cross the blood brain barrier, even in the presence of inflamed meninges.

A loading dose is often administered in the critically ill; 1.5 to 2 mg/kg for gentamicin or tobramycin and 7.5 to 15 mg/kg for amikacin (Table 7). Interpatient variability in volume of distribution and renal function in the critically

ill population necessitates monitoring of aminoglycoside concentrations in the serum. Ideally, peak concentrations should be obtained 30 minutes after a 30-minute infusion. Trough concentrations should be drawn as close as possible prior to the start of the next dose. Recent studies suggest that single daily dosing is at least as effective as traditional dosing (due to the prolonged post-antibiotic effect) and may be less toxic (because the kidneys are allowed some recovery time between doses, when the blood concentration is low) (45).

Antimicrobial Activity/Spectrum/Resistance

Aminoglycosides are active against aerobic gram-negative bacilli and certain mycobacteria (including *Mycobacterium tuberculosis*) and have in vitro activity against many Staphylococcus species. Despite in vitro activity, aminoglycosides are not useful as single agents in treating gram-positive infections. However, aminoglycosides can be used synergistically with either beta-lactams or glycopeptides in patients with either *S. aureus* or enterococcal infections. *Burkholderia* (formerly *Pseudomonas cepacia*) and *Stenotrophomonas* (formerly *Pseudomonas* or *Xanthomonas*) *maltophilia* are typically resistant to all aminoglycosides. This rather narrow spectrum of activity is reflected in Tables 1 and 2 showing aminoglycosides as mainly alternative agents to first-line therapy.

The most common mechanism of aminoglycoside resistance is the production of plasmid-mediated aminoglycoside-modifying enzymes. Resistance of enterococci to gentamicin was first reported in the United States 15+ years ago. A survey of eight United States tertiary-care hospitals demonstrated that 25% of enterococci had high-level resistance to gentamicin. These organisms are generally resistant to all other aminoglycosides, but occasionally are susceptible to streptomycin.

Adverse Effects and Drug Interactions

⚡ All aminoglycosides are nephrotoxic and ototoxic and can prolong the duration of neuromuscular blockade drugs. ⚡ Aminoglycosides are reabsorbed by the proximal tubule accumulating in the renal cortex. This accounts for the nephrotoxicity, which is reportedly most common for gentamicin and least common for streptomycin, with amikacin and tobramycin being intermediate. Clinical nephrotoxicity does not usually occur until after at least 1 week of therapy, and is nonoliguric. Nephrotoxicity is typically reversible; however, ototoxicity (either vestibular or auditory) is generally permanent. Potentiation of neuromuscular blockade may also occur with the aminoglycosides, even after copious peritoneal irrigation with an aminoglycoside

Table 7 Aminoglycosides: Selected Dosing and Need for Adjustment Based Upon Renal or Hepatic Dysfunction

Aminoglycoside drug name	Typical adult IV dose range and intervals	Requires dose adjustment for renal insufficiency (CrCl <30 mL/min)	Requires dose adjustment for hepatic failure
Gentamicin	1.5–2.5 mg/kg q12 hr or 5 mg/kg q24 hr	Yes	No
Tobramycin	1.5–2.5 mg/kg q12 hr or 5 mg/kg q24 hr	Yes	No
Amikacin	7.5 mg/kg q12 hr or 15 mg/kg q24 hr	Yes	No
Streptomycin	10–15 mg/kg q24 hr	Yes	No

Abbreviation: IV, intravenously.

(Volume 2, Chapter 6). It is treated primarily by supportive means (airway protection or ventilation).

The ototoxicity seen with furosemide is additive when administered concomitantly with aminoglycosides. Bumetanide is less ototoxic and should be considered when concomitant use of aminoglycosides and diuretics are needed.

Age greater than 60 and co-administration of other nephrotoxic drugs can exacerbate the nephrotoxicity due to aminoglycosides. Examples of these drugs include: amphotericin B, vancomycin, parenteral bacitracin, capreomycin, cidofovir, cisplatin, cyclosporine, foscarnet, ganciclovir, IV pentamidine, polymyxin B, streptozocin, or tacrolimus.

Therapeutic/Clinical Uses

Gentamicin

Gentamicin is used alone primarily for urinary tract infections. It is also typically used in conjunction with extended-spectrum penicillins for nosocomial infections caused by *Enterobacter* spp. and *P. aeruginosa*. Combination therapy including an aminoglycoside with agents that provide gram-positive or anaerobic activity is frequently used in potentially polymicrobial infections when gram-negative rods may be playing a role. An aminoglycoside is used in combination therapy with either ampicillin or vancomycin for several different types of endocarditis, most commonly those that are due to enterococci.

Tobramycin

Tobramycin has essentially the same parenteral uses as gentamicin. It has greater activity against *Acinetobacter* spp. and *P. aeruginosa* but less activity against *Serratia marcescens* than gentamicin does. If organisms are resistant to gentamicin, they will likely be resistant to tobramycin. Inhaled tobramycin has been associated with improved pulmonary function and decreased hospitalization in patients with cystic fibrosis.

Amikacin

Amikacin is useful primarily for organisms that are resistant gentamicin and tobramycin. It is also used in combination with other antibiotics, for example, for infections due to *Nocardia asteroides* and occasionally for infections due to *M. tuberculosis* or *M. avium* complex.

Streptomycin

Streptomycin is sometimes used (as part of combination therapy) in the treatment of multidrug-resistant tuberculosis

and may be useful in the treatment of some gentamicin-resistant enterococcal infections. It is also the drug of choice for several potential bacterial agents in bioterrorism, such as tularemia and plague, although gentamicin can be used alternatively.

TETRACYCLINES AND GLYCYLCYCLINES

History/Description

The tetracyclines were isolated from *Streptomyces* spp., first used clinically over 50 years ago. ♂ **Tetracycline has a broad spectrum of activity against gram-positive, gram-negative, and anaerobic bacteria as well as rickettsiae, mycoplasma, chlamydiae, protozoa, actinomycetes, and even certain viruses.** ♂ Tetracyclines are infrequently used in the ICU setting. However, when they are employed, it is usually to combat pneumonia due to presumed or known "atypical" agents (Table 8). Doxycycline and, to a lesser extent, minocycline are the most commonly used drugs of this class. The tetracyclines are still commonly used for community acquired pathogens, and have recently been reviewed in depth (46,47).

Mechanism of Action, Pharmacology, Administration, and Dosage

The tetracyclines are similar in mechanism of action to aminoglycosides, as both antimicrobials inhibit bacterial protein synthesis at the ribosomal level. However, in regard to spectrum of activity, the tetracyclines more closely resemble the macrolides. The tetracyclines are typically bacteriostatic rather than bactericidal. Tetracycline is excreted in the urine and should be avoided in renal insufficiency, because high concentrations of the accumulated drug are hepatotoxic. In contrast to tetracycline, doxycycline, and minocycline are eliminated through hepatobiliary processes and can be used in patients with renal insufficiency.

Doxycycline and other tetracyclines can be administered either parenterally or orally, and because of the long half-life, can be administered once or twice daily. Refer to Table 9 for tetracycline dosing and need for dose adjustment.

Antimicrobial Activity/Spectrum/Resistance

The tetracyclines are currently utilized for the empiric treatment of community-acquired pneumonia because of their activity against both many pyogenic bacteria and "atypical" organisms, such as *Mycoplasma* spp., *Chlamydia* spp., or *Legionella* spp. They also have utility in the treatment of infections

Table 8 Antimicrobial Drugs of Choice Against Atypical Organisms

Microorganisms	Drug of choice	Alternative agents
<i>Mycoplasma pneumoniae</i>	Azithromycin or a tetracycline	Fluoroquinolone, erythromycin, clarithromycin
<i>Chlamydia psittaci</i>	Fluoroquinolone or doxycycline	Chloramphenicol
<i>Chlamydia pneumoniae</i>	Azithromycin or tetracycline	Fluoroquinolone, erythromycin, clarithromycin
<i>Ehrlichia</i> spp.	Doxycycline	
<i>Rickettsia</i> spp.	Doxycycline	
<i>Borrelia burgdorferi</i> (Lyme disease)	Amoxicillin or doxycycline	Chloramphenicol, rifampin, fluoroquinolone
<i>Leptospira</i>	Penicillin	Ceftriaxone, cefotaxime, azithromycin, clarithromycin
<i>Treponema pallidum</i> (syphilis)	Penicillin	A tetracycline, ceftriaxone
<i>Actinomyces</i> spp.	Penicillin	Ceftriaxone, a tetracycline, erythromycin
<i>Nocardia</i> spp.	Co-trimoxazole	A tetracycline, erythromycin, clindamycin
		A tetracycline, carbapenem, linezolid

Table 9 Antibacterial Agents: Requiring Selected Dosing and Need for Adjustment Based Upon Renal or Hepatic Dysfunction

Misc. drug name	Typical adult IV dose range and intervals	Requires dose adjustment for renal insufficiency (CrCl <30 mL/min)	Requires dose adjustment for hepatic failure
Mimocycline	100 mg every 12 hr	No	±
Doxycycline	100 mg every 12 hr	No	±
Erythromycin	0.5–1 g every 6 hr	No	±
Azithromycin	0.25–0.5 g every 24 hr	No	No
Clarithromycin	500 mg orally every 12 hr	Yes	No
Clindamycin	600 mg every 8 hr	No	No
Metronidazole	500 mg every 8–12 hr	No	Yes
Quinupristin/dalfopristin	7.5 mg/kg every 8 hr	No	±
Linezolid	600 mg every 12 hr	No	±
Vancomycin	15 mg/kg every 12 hr	Yes	No
Daptomycin	4–6 mg/kg every 24 hr	Yes	No
Rifampin	600 mg every 24 hr	No	Yes
Tmp/sulfamethoxazole	5 mg/kg of tmp every 8–12 hr	Yes	±
Aminoglycosides	Table 7	Yes	No
Tigecycline	100 mg once followed by 50 mg every 12 hr	No	Yes

Note: ± indicates although specific dosage guidelines are not available, a reduced dosage may be necessary.
Abbreviations: Tmp, trimethoprim; IV, intravenously.

due to *Brucella* spp., rickettsiae, chlamydiae, syphilis, *Borrelia burgdorferi* (the agent of Lyme infection), *Vibrio* spp., *Yersinia* spp., *Francisella tularensis*, *Leptospira* spp., and genital infections. The tetracycline group is also useful in the treatment of some nontuberculous mycobacterial infections (such as *Mycobacterium marinum*). Tetracyclines were originally the only drugs available to treat VRE, however, linezolid, daptomycin, and quinopristin/dalfopristin have been recently used as well.

Adverse Effects and Drug Interactions

The tetracyclines are generally well tolerated with two important exceptions: photosensitivity and discoloration of developing teeth and bones in children. Minocycline is also associated with vestibular toxicity and a blue-tinged hyperpigmentation of the skin and mucous membranes.

Milk, antacids, iron supplements, and probably other agents with divalent cations decrease the gastrointestinal absorption of orally administered tetracyclines and should be ingested several hours before or after the administration of tetracycline (which is best taken on an empty stomach). These oral divalent cations have less effect on the oral absorption of doxycycline and minocycline.

Therapeutic/Clinical Uses

As a result of the broad spectrum of the tetracyclines as noted above, these agents are useful in a wide variety of infections; however, they are rarely indicated as the drug of choice in the critically ill patient except for the treatment of rickettsial infections and pulmonary infections due to "atypical" agents (Table 8).

Tigecycline, a glycine derivative of minocycline, received FDA approval for skin and skin structure infections and complicated intra abdominal infections in 2005. Like the tetracyclines, tigecycline has a broad spectrum of activity (48,49). It is active against gram-positive organisms,

gram-negative aerobes, anaerobes, and "atypical" organisms like Chlamydiae and Mycoplasma. It also has activity against organisms that are tetracycline resistant and is also active against MRSA, MRSE, VRE, and penicillin-resistant pneumococci. A notable gap in its spectrum is a lack of activity against *P. aeruginosa*, which could limit the use of tigecycline in the treatment of nosocomial infections, especially HAP. However, since it is much more potent than other tetracyclines, which are bacteriostatic, tigecycline will likely find use in non-pseudomonal HAP. The major side effect noted in early phase trials is nausea and vomiting in patients (20–35%). Tigecycline is only available as an intravenous preparation due to poor oral bioavailability. Its potential place in the therapeutic armamentarium is yet undefined.

MACROLIDES

History/Description

Erythromycin was the first clinically available macrolide antibiotic, and was introduced clinically in the 1950s. Erythromycin is derived from the soil fungus, *Streptomyces erythreus*. Modifications of the erythromycin chemical structure have led to two new macrolides (azithromycin and clarithromycin). Both azithromycin and clarithromycin possess better gastrointestinal tolerability and a somewhat broader spectrum of activity than erythromycin, although at a greatly increased cost. The macrolides are reviewed in several recent articles (50–52).

Mechanism of Action, Pharmacology, Administration, and Dosage

The macrolides all act at the ribosome by inhibiting RNA-dependent protein synthesis. Azithromycin and clarithromycin are acid-stable and well absorbed from the gastrointestinal tract, irrespective of the presence of food.

Erythromycin, which is inactivated by stomach acids, requires enteric coating to increase its efficacy. All macrolides are rapidly absorbed and concentrate well within tissues, including phagocytes. The high concentration of macrolides within phagocytes serves as a delivery system of the drug to the site of infection. ♂ **Azithromycin has an extremely long intracellular dwell time, permitting once daily (or less often) dosing.** ♂ Indeed, azithromycin is often used once weekly for the prophylaxis of mycobacterial infections in patients with AIDS.

Various erythromycin products are available for both oral and parenteral administration. Intravenous administration of erythromycin is associated with thrombophlebitis, and intramuscular injections should be avoided due to pain. Oral and intravenous azithromycin are also available. A parenteral form of clarithromycin is currently not available. Dosing guidelines are shown in Table 9.

Antimicrobial Activity/Spectrum/Resistance

Erythromycin, clarithromycin, and azithromycin all have bacteriostatic activity against gram-positive organisms, such as *Streptococcus pneumoniae* and some *S. aureus*. These agents also have good in vitro and clinical activity against *Mycoplasma*, *Legionella*, syphilis, and chlamydiae. Of note, both clarithromycin and azithromycin have activity against some mycobacteria (including *M. avium* complex) and *Helicobacter* spp. Erythromycin lacks activity against *H. influenzae*, whereas both azithromycin and clarithromycin are efficacious against this agent. The macrolides are frequently used in patients with allergies to beta-lactams, especially for infections due to gram-positive bacteria. However, they have very limited activity against MRSA and enterococcus, and a significant proportion of *S. pneumoniae* are resistant to the macrolides in some locales.

Adverse Effects and Drug Interactions

Gastrointestinal intolerance is a frequent complication of oral erythromycin products, whereas the other macrolides tend to be much better tolerated. One advantage of azithromycin over the other macrolides is the absence of clinically significant drug–drug interactions involving the cytochrome P-450 system (CP450) (Volume 2, Chapter 4).

Therapeutic/Clinical Uses

Macrolides are commonly used for community-acquired pneumonias and in patients who are allergic to penicillins. The promotility side effect of low-dose erythromycin is increasingly utilized as a promotility agent in critically ill patients with gastroparesis.

LINCOSAMIDES (CLINDAMYCIN)

History/Description

Clindamycin, a lincosamide derivative, has been in clinical use since the mid-1960s. Although clindamycin is associated with *C. difficile* colitis, it remains one of the mainstays in the treatment of serious anaerobic infections, and as an alternative agent for some *S. aureus* infections (51,53,54).

Mechanism of Action, Pharmacology, Administration, and Dosage

Clindamycin inhibits RNA-dependent protein synthesis acting at the ribosomal level (infusion similar to macrolides). Although oral and intravenous preparations of clindamycin

penetrate most body tissues (including lung, liver, bone, and extra-cranial abscesses), it does not easily cross the blood-brain barrier or enter the CSF, even when the meninges are inflamed. Thus, metronidazole, which fully penetrates the CSF, should be used for any CNS infections involving anaerobic organisms (other than CNS toxoplasmosis—which can be treated with clindamycin). Dosing guidelines are shown in Table 9.

Antimicrobial Activity/Spectrum/Resistance

Clindamycin has a spectrum of activity that includes many anaerobes, especially oral flora; some aerobic gram-positive cocci, including most strains of pneumococci; other streptococci; *S. aureus*; *Pneumocystis carinii*; and *Toxoplasma gondii*. Clindamycin has no activity against enterococci and has limited activity against most MRSA. The majority of aerobic gram-negative bacilli are intrinsically resistant to clindamycin. Most intestinal *Bacteroides* spp., especially of *B. fragilis* are resistant to clindamycin (55). Clindamycin, therefore, should not be a first-line antianaerobic agent to treat infections below the diaphragm.

Adverse Effects and Drug Interactions

Clindamycin exerts a direct muscular depressant effect, and may prolong the duration of neuromuscular blockage (56). Diarrhea is a common side effect of clindamycin, even in the absence of colitis, and the potential for the development of *C. difficile* colitis makes the use of this antibiotic complicated, limiting its use to severe infections with clear indications for use.

Clindamycin has no clinically significant drug–drug interactions.

Therapeutic/Clinical Uses

Clindamycin is used most commonly for infections outside of the CNS (except cerebral toxoplasmosis) that are thought to include anaerobes, especially *B. fragilis* and other penicillin-resistant anaerobes. Clindamycin is utilized in some pulmonary infections, especially aspiration pneumonia that is community-acquired and also as a useful alternative to penicillin.

Clindamycin has been successfully used in the treatment of pelvic inflammatory disease (PID) for years. This success probably relates to the fact that vaginal anaerobic flora are more similar to oral anaerobes than to colonic anaerobes in general. However, if the PID infection involves *B. fragilis*, metronidazole is a better choice. Although sexually transmitted pathogens can cause PID, these infections tend to become polymicrobial, involving aerobes and anaerobes. Clindamycin is frequently used with other antibiotics that have gram-negative bacillary activity. Since clindamycin is a protein synthesis inhibitor and can act even when cells are in stationary phase, it has utility in the treatment of bacterial toxidromes and in situations such as necrotizing fasciitis. ♂ **Because of its gram-positive and anaerobic coverage, clindamycin is useful (with combination gram-negative therapy) for necrotizing fasciitis, most oral and vaginal anaerobic infections, and diabetic foot infections, which tend to be polymicrobial and virulent.** ♂

METRONIDAZOLE

History/Description

Metronidazole is a nitroimidazole drug first synthesized in the 1950s and was originally recognized as being effective

against certain protozoa. In the 1960s metronidazole was recognized to also possess excellent anaerobic antimicrobial activity (53,57). ⚡ **Metronidazole is indicated for the treatment of serious polymicrobial infections involving anaerobes (e.g., necrotizing fasciitis and infections involving contamination from the GI tract). Importantly, other agents with aerobic gram-positive and gram-negative coverage must be co-administered.** ⚡

Mechanism of Action, Pharmacology, Administration, and Dosage

Metronidazole enters the cell by passive diffusion where its nitro group is reduced by electron transport proteins with low redox potential. This process produces metabolites that alter the helical structure of DNA and subsequently causes cell death (58).

Metronidazole is rapidly absorbed in the gut. Indeed, serum levels are similar following oral and intravenous administration. Although metronidazole is almost completely absorbed after oral administration, critically ill patients should receive therapy via the intravenous route until stable (59). When the patient is stable, and the gut is functional, administration should be converted to the enteral route for cost saving since it is nearly 100% bioavailable. The liver metabolizes metronidazole into a water-soluble metabolite, and both this metabolite and the un-metabolized metronidazole are excreted in the urine. No dosage adjustment is required in those with renal insufficiency, but dosage should be reduced in patients with hepatic insufficiency. Therapeutic drug levels are attained in most tissues; excellent levels are found in the CSF.

In severe anaerobic infections, metronidazole is administered as a loading dose of 15 mg/kg intravenously followed by 7.5 mg/kg every six to eight hours. This typically equates to 1 g followed by 500 mg every six to eight hours.

Antimicrobial Activity/Spectrum/Resistance

Metronidazole is active against certain protozoa, including *Trichomonas*, *Giardia*, and *Entamoeba* however; its primary role in the critically ill patient is as an extremely active agent against obligate anaerobic bacteria and is the antimicrobial agent most reliably active against *B. fragilis* (60). Resistance has been reported in Europe and Africa but is very uncommon (53). When metronidazole resistance does occur, it is most commonly attributable to the presence of one of the five known *nim* nitroreductase genes (61). Metronidazole resistance had not previously been reported in *B. fragilis* isolates from the Western Hemisphere, recently a serious infection involving a metronidazole-resistant *B. fragilis* isolate was recovered from a patient in Seattle, Washington in 2004 with the *nimA* nitroreductase gene (61).

Adverse Effects and Drug Interactions

The most severe adverse effect seen with metronidazole, although rare, involves the central nervous system and may include seizures, encephalopathy, cerebellar dysfunction, and peripheral neuropathy (57). More commonly, metronidazole causes minor gastrointestinal side effects such as nausea, diarrhea, a metallic taste, stomatitis, and dry mouth (57). Alcohol should be avoided while receiving metronidazole because it can induce a disulfiram-like reaction (57,62). Metronidazole inhibits the metabolism of warfarin and will prolong the prothrombin time and INR in patients taking coumarin-type anticoagulants (63).

Therapeutics/Clinical Use

In general, as a result of its spectrum of activity, metronidazole is extremely useful in most anaerobic infections with the important exceptions of those due to *Actinomyces* spp. and *Propionibacterium acnes* (57). The excellent penetration of metronidazole into all tissues combined with its bactericidal activity makes it effective for the treatment of most serious anaerobic infections (57). Many serious anaerobic infections are polymicrobial, therefore, additional agents with better coverage against gram-positive aerobes and gram-negative organisms are also necessary. ⚡ ***B. fragilis* is probably the most frequently encountered clinically significant anaerobe where metronidazole should be considered the drug of choice, especially in intra-abdominal infections (57).** ⚡ Metronidazole is also the drug of choice for the treatment of pseudomembranous colitis due to *C. difficile* (54). Oral vancomycin is an alternative in seriously ill patients with pseudomembranous colitis.

QUINUPRISTIN/DALFOPRISTIN (SYNERCID®)

History/Description

The evolution of multi-drug resistant bacteria, including MRSA and VRE faecium, has created a pressing need for effective alternative antibiotics, hence the utility of the streptogramins (i.e., quinupristin/dalfopristin), linezolid, and daptomycin.

The streptogramins are a family of compounds isolated from *Streptomyces pristinaespiralis*. The family is divided into group A and group B based on molecular structure. Dalfopristin is a derivative of a group A streptogramin, and quinupristin is a group B streptogramin. These two streptogramins have been combined in a commercially available injectable form at a 30:70 weight-to-weight ratio. Individually, these compounds demonstrate only modest in vitro activity. However, the combination is synergistic. Unfortunately, in vitro studies also demonstrate that the combination of quinupristin and dalfopristin is not bactericidal against all species and strains of common gram-positive organisms.

Quinupristin/dalfopristin, a combination product known as "Synercid," has demonstrated activity against most strains of aerobic gram-positive microorganisms, both in vitro and in clinical infections, including; *E. faecium* (vancomycin-resistant and multi-drug resistant strains only), *S. aureus* (both MSSA and MRSA), and *Streptococcus pyogenes* (group A beta-hemolytic streptococci) (64,65). This compound is bacteriostatic against *E. faecium* and bactericidal against strains of methicillin-susceptible and methicillin-resistant *Staphylococci* spp. Importantly, dalfopristin/quinupristin has no activity against *Enterococcus faecalis*. A post-antibiotic effect has been demonstrated for *S. aureus*: seven hours for methicillin-susceptible strains; five hours for methicillin-resistant strains. Since the mode of action of streptogramins differs from other classes of antibacterial agents, there is no cross-resistance.

Mechanism of Action, Pharmacology, Administration, and Dosage

Quinupristin and dalfopristin bind to sequential sites located on the 50S subunit of the bacterial ribosome. Dalfopristin binding causes a conformational change in the ribosome that subsequently increases the binding of quinupristin. The binding of both agents to the ribosome constricts the exit channel on the ribosome through which nascent polypeptides

are extruded; proper functioning of the ribosome is blocked and transfer RNA (tRNA) synthetase activity is inhibited leading to a decrease in free tRNA within the cell. Without these tRNAs, the bacterial cell cannot properly incorporate amino acids into peptide chains leading to bacterial cell death.

Quinupristin/dalfopristin undergoes hepatic metabolism, and both compounds have active metabolites. However, no increase in adverse events has been reported in patients with hepatic impairment, and no dosage reduction is required in these patients. The parent drugs and major metabolites are eliminated primarily by fecal excretion (75%) with a small portion of unchanged quinupristin and dalfopristin (15–19%) eliminated renally. In patients with a creatinine clearance <29 mL/min, a 30% increase in the combined AUC of quinupristin/dalfopristin and their metabolites has been observed, but the manufacturer has not established guidelines for dosage reduction. The manufacturer's recommended intravenous dose of quinupristin/dalfopristin in adults is 7.5 mg/kg given over 60 minutes every eight hours preferably through a central line.

Antimicrobial Activity/Spectrum/Resistance

Resistance to the streptogramins has been reported (66,67). The most common expression of bacterial resistance to streptogramins is through conformational alterations in ribosomal target binding sites. However, it appears that multiple point mutations are required for drug resistance to this combination product to develop.

Adverse Effects and Drug Interactions

The most common adverse effects with quinupristin/dalfopristin are infusion-site reactions. Non-infusion related reactions including nausea, diarrhea, vomiting, rash, headache, pain, and pruritus were reported with similar frequency as comparator antibiotics in one trial. Elevations in liver enzymes (2–7%), increases in total and direct bilirubin (1–5%), thrombocytopenia (2%), and decreases in hemoglobin of <8–mg/dl (2.6%) have also been reported.

Quinupristin/dalfopristin is an inhibitor of Cytochrome P450 (CP450) 3A4 enzyme. One study demonstrated a two-fold increase in cyclosporine levels within two to five days of concomitant use. Caution is recommended when concomitantly administering other agents that are eliminated via the CP450-3A4 isoenzyme pathway with quinupristin/dalfopristin (Volume 2, Chapter 4).

Therapeutic/Clinical Uses

Quinupristin/dalfopristin is the most expensive parenteral antibacterial currently on the market. **The greatest utility of quinupristin/dalfopristin, daptomycin, and linezolid is in the management of patients with multi-resistant enterococci (VRE) or MRSA infections for which limited alternatives exist.** The treatment of VRE infections has been recently reviewed (68,69).

LINEZOLID (ZYVOX®)

History/Description

Linezolid is one of a new class of synthetic antibiotics known as fluorinated oxazolidinones (70,71). This drug is designed to target MRSA; it also provides good activity against other gram-positive organisms, including penicillin-resistant

pneumococci and VRE (72). This drug now provides an alternative to vancomycin therapy in an oral formulation.

Mechanism of Action, Pharmacology, Administration, and Dosage

Linezolid inhibits bacterial protein synthesis by interfering with translation. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit; this action prevents the formation of a functional 70S initiation complex, an essential step in the bacterial translation process. The action of linezolid is considered to be bacteriostatic against Staphylococci and Enterococci, but is bacteriocidal against the majority of Streptococcal strains tested.

Following oral administration, absorption of linezolid appears to be rapid with a peak plasma concentration (t_{max}) of one to two hours (73). The oral bioavailability is approximately 100% and as such linezolid may be administered orally or intravenously without dosage adjustment (73). Linezolid is distributed extensively to various tissues. Linezolid appears to partition into the central nervous system at a CSF: serum ratio of 0.65:1; it has been used to successfully treat ventriculoperitoneal shunt infections caused by VRE or coagulase-negative Staphylococci. Of major importance in critical care, linezolid penetrates into bronchoalveolar lavage fluid and lung tissue more effectively than vancomycin (74).

The recommended adult dosage is 600 mg intravenous or orally every 12 hours for all indications except uncomplicated skin and soft-tissue infections, for which the recommended dosage is 400 mg orally every 12 hours. Elimination of linezolid is primarily (65%) nonrenal. Clearance is mediated by non-enzymatic chemical oxidation, which results in the formation of two major inactive metabolites, which are excreted renally (75).

Dosage adjustments are not necessary in renal insufficiency or mild to moderate hepatic dysfunction. Approximately 30% of a dosage of linezolid is removed by hemodialysis. For this reason, patients should receive their linezolid doses post-dialysis.

Antimicrobial Activity/Spectrum/Resistance

Soon after linezolid became FDA-approved in the US, reports of linezolid-resistant VRE organisms were identified at several institutions. Resistance with linezolid has been observed in 15 patients with enterococcal infections, and a vancomycin-resistant strain of *E. faecium* with reduced susceptibility to linezolid (MIC = 8 mg/mL) has been isolated. Preliminary reports suggest that most cases of resistance to linezolid occur when the drug is used for prolonged periods of time in patients with prosthetic devices. Resistance to linezolid is usually associated with single-point mutations in 23S rRNA. Studies suggest the frequency of spontaneous resistance to linezolid is <10⁻⁹.

Adverse Effects and Drug Interactions

The most frequently reported adverse events with linezolid in one study were diarrhea (8.3%), nausea (6.6%), headache (6.4%), and vomiting (4.3%). In another study, tongue discoloration (2.5%), oral candidiasis (2.3%), and injection-site pain (1.4%) were also reported. Thrombocytopenia (platelet count <75% of the lower limit of normal and/or baseline) was reported in 2.4% of patients who received linezolid in clinical trials. Linezolid-related thrombocytopenia appears to be associated with prolonged duration of

therapy (>2 weeks) and is generally reversible on discontinuation.

Linezolid is metabolized via oxidation of its morpholine ring, independent of CP450 activities. It is 31% protein bound; therefore, interactions via displacement from protein binding sites are unlikely. Linezolid is a weak, reversible inhibitor of human monoamine oxidase A. Consequently, it has the potential to interact with adrenergic and serotonergic agents, leading to hypertensive crises (Volume 2, Chapter 17) and serotonin syndrome (Volume 1, Chapter 40 and Volume 2, Chapter 46). Mean increases in systolic blood pressure of 32 and 38 mmHg have been observed in normotensive subjects taking linezolid concomitantly with pseudoephedrine and phenylpropanolamine, respectively.

Therapeutic/Clinical Uses

Linezolid is an expensive drug; one day of linezolid costs roughly the same amount as 500 days of either doxycycline or co-trimoxazole. Although this antibiotic represents the first in a unique class of antibiotics (the oxazolidinones), more clinical experience and formal pharmacoeconomics data should be obtained prior to its widespread clinical use. Linezolid should be reserved for the treatment of documented serious VRE or MRSA infections, or when oral therapy is an option. Since it appears to achieve high levels in the lungs, it may soon become the drug of choice to treat MRSA pneumonia (74).

VANCOMYCIN

History/Description

Vancomycin is a bactericidal glycopeptide derived from the soil fungus *Streptomyces orientalis* and was first introduced in 1956. Within two years, vancomycin use was superseded by methicillin and cephalothin, which had fewer side effects. In the late 1970s, MRSA began to emerge, and vancomycin returned to the clinical arena to treat these threats. Recent improvements in manufacturing have increased its purity and reduced the nephrotoxicity of vancomycin (75–78). However, the histaminereleasing effect responsible for “red man” syndrome and hypotension during administration still persist. Teicoplanin, a related compound, is at least as efficacious and less toxic. Teicoplanin has been used for years in Europe, but it is not currently available in the US. ♂ **Vancomycin is most often used parenterally to treat MRSA, empirically in life-threatening infections, and orally for *C. difficile* colitis.** ♀

Mechanism of Action, Pharmacology, Administration, and Dosage

Vancomycin exerts its effect by binding to the precursor units of bacterial cell walls, known as peptidoglycans, inhibiting their synthesis. This binding occurs at a different site of action from that of penicillin. The net result is an alteration of bacterial cell wall permeability. In addition, RNA synthesis is inhibited. Gram-negative organisms are not sensitive to vancomycin, because porin channels in their cell wall do not accommodate the large, bulky vancomycin molecule.

Vancomycin is about 55% protein bound. Vancomycin penetrates most body tissues including the brain when the meninges are inflamed. Vancomycin also distributes well into pericardial, pleural, ascitic, and synovial fluids. Intravenous vancomycin is primarily excreted unchanged by the kidneys. Vancomycin has poor oral bioavailability with oral

doses remaining intraluminal in the intestine until eliminated in the feces; this also explains its oral use in *C. difficile* colitis. Vancomycin has a half-life of approximately six hours in a patient with normal renal function. However, in anuric patients, the half-life can be prolonged to approximately 7.5 days. Vancomycin is not removed by hemodialysis or peritoneal dialysis, unless F60 or F80 polysulfone filters are used (Volume 2, Chapter 43). In patients with normal renal function, vancomycin is dosed at 1 g IV every 12 hours, and levels are tested. Teicoplanin is dosed on an every 24-hour basis. In those patients with known or suspected renal impairment, an initial vancomycin dose of 15 mg/kg should be given, and the dosage interval increased. The appropriate dosage interval should be further determined using therapeutic drug level monitoring. When vancomycin is given with an aminoglycoside, increased incidence of nephrotoxicity is possible. For pseudomembranous colitis, a dosage of 125–500 mg orally every six hours for 7–10 days is appropriate.

Antimicrobial Activity/Spectrum/Resistance

Vancomycin is bactericidal against essentially all staphylococci (both *S. aureus* and coagulase-negative Staphylococci), all *S. pneumoniae*, *S. pyogenes*, and *S. viridans*. It is bacteriostatic against most Enterococcus and most *Corynebacterium* spp. A few anaerobes are susceptible, but virtually no gram-negative organisms are susceptible to vancomycin. Vancomycin has achieved a prominent role in therapy of critically ill patients due to the large prevalence of MRSA in hospitals. To an increasing extent, critically ill patients have temporary or permanent foreign bodies implanted as pacemakers, vascular access, valves, or shunts. These devices are particularly predisposed to infection by Staphylococci, including *S. aureus* and coagulase-negative Staphylococci, an increasing fraction of which is methicillin-resistant.

Vancomycin intermediate-susceptible *S. aureus* (VISA) is used to describe decreased susceptibility of *S. aureus* to vancomycin (79,80). In 1997, the first strain of *S. aureus* with reduced susceptibility to vancomycin was reported from Japan (81). The Clinical and Laboratory Standards Institute (CLSI) defines Staphylococci requiring concentrations of vancomycin of ≤ 4 mcg/mL for growth inhibition as susceptible, those requiring 8 to 16 mcg/mL as intermediate (VISA) (79,80), and those requiring concentrations of >32 mcg/mL as resistant (VRSA) (82). Implications of multi-drug resistant organisms make therapeutic choices much more difficult and reinforce the need to control the use of vancomycin and other antibiotics (16). Infections with these vancomycin resistant microorganisms are usually sensitive to linezolid, daptomycin, or dalbapristin/quinupristin.

The proportion of Enterococci isolated from ICUs that were resistant to vancomycin increased from 0.3% in 1989 to almost 24% in 1998. Enterococci are able to build cell walls in the presence of glycopeptide antibiotics because they can bypass an intermediate molecule to which the glycopeptide binds (83). Risk factors for the emergence of VRE include exposure to broad spectrum cephalosporins, vancomycin, or antibiotics with significant anaerobic activity; and prolonged hospital and/or ICU stay. The empiric use of vancomycin should be limited to life threatening infections in order to reduce the emergence of VRE.

Adverse Effects and Drug Interactions

Vancomycin is now considered approximately 95% free of impurities; therefore the incidence of adverse effects has declined (84). However, phlebitis still occurs with

peripherally administered vancomycin in approximately 13% of patients. Hypotension, flushing, tingling, and erythema affecting upper trunk, face, and arms (red person syndrome) are associated with rapid infusion in 3% to 11% of patients, especially if 1-g doses are used. Treatments with fluid administration, antihistamines, and corticosteroids have been suggested, as well as slowing the infusion. Rash unrelated to "red person syndrome" is also seen in about 2% to 5% of patients. The rash is often described as maculopapular, but rare cases of Stevens-Johnson have been reported. Neutropenia occurs in approximately 2% of patients (84), the onset typically being delayed up to 30 days after commencing the drug. Nephrotoxicity and ototoxicity are uncommon if peak serum levels are maintained <50 mcg/mL, but more likely to occur if vancomycin is administered with other nephro- or ototoxic compounds, and more common in critically ill patients.

Drugs that increase the risk of nephrotoxicity when co-administered with vancomycin include: amphotericin B, aminoglycosides, parenteral bacitracin, capreomycin, cidofovir, cisplatin, cyclosporine, foscarnet, ganciclovir, IV pentamidine, polymyxin B, streptozocin, and tacrolimus. The combined use of vancomycin and cidofovir is contraindicated. Vancomycin should be discontinued seven days prior to beginning cidofovir.

Orally administered vancomycin should not be used with cholestyramine or colestipol. These anion-exchange resins can bind vancomycin and reduce its effectiveness. Since these drugs are sometimes used to treat *C. difficile* colitis by binding the toxin in the intestinal lumen, patients may be taking vancomycin and one of the resins simultaneously. If patients must take both drugs, doses should be administered several hours apart.

Vancomycin should be used cautiously with other ototoxic drugs such as aminoglycosides, aspirin or other salicylates, capreomycin, ethacrynic acid, furosemide, or paromomycin. Vancomycin may potentiate the neuromuscular effects of nondepolarizing neuromuscular blockers (Volume 2, Chapter 6). Vancomycin, when used concomitantly with metformin, may increase the risk of lactic acidosis. Vancomycin can decrease metformin elimination by competing for common renal tubular transport systems, necessitating careful monitoring while on concurrent therapy.

Therapeutic Drug Level Monitoring

The ideal vancomycin-dosing regimen is one that results in peak vancomycin concentrations that are less than 30 to 50 mg/L and trough concentrations that are in the range of 5 to 15 mg/L. Therapeutic drug monitoring of vancomycin remains controversial (85). Vancomycin exhibits concentration-dependent killing, requiring a serum concentration >1 mg/L. Therefore, higher concentrations are not necessarily associated with improved bactericidal effects (especially in the lung)! For MRSA pneumonia vancomycin troughs should be >15 to 20 mg/L. Most clinicians believe patients at high risk for therapeutic failure or potential toxicity should have both peak and trough values monitored. These patients include the elderly, those with poor renal function, or patients with suspected alteration in their volume of distribution; this includes the critically ill.

Therapeutic/Clinical Uses

The primary indication for vancomycin is for MRSA infections, and empiric administration in critically ill patients with significant infections or sepsis until culture results

return. Other indications for vancomycin include Staphylococcal and Streptococcal infections in patients allergic to penicillins, and as an alternative to penicillin for the prophylaxis of bacterial endocarditis. Vancomycin is being used in conjunction with ceftriaxone in locales with high prevalence rates of highly penicillin-resistant pneumococcal meningitis. For organisms susceptible to beta-lactams, clinical experience has demonstrated improved patient outcome with the use of beta-lactams rather than with vancomycin. Vancomycin is also useful in oral therapy against *C. difficile* colitis.

DAPTOMYCIN

History/Description

Daptomycin is the first antibacterial agent from a novel class of drugs, the cyclic lipopeptides (derived from *Streptomyces roseosporus*). Discovered more than 20 years ago, its clinical research was halted due to concerns of skeletal muscle toxicity. However, development resumed in response to the increasing demand for bactericidal antibiotics effective against VRE and VRSA (86). Daptomycin is now approved for the treatment of complicated skin and skin structure infections caused by gram-positive bacteria. It recently received FDA approval for use in the treatment of bacteria and endocarditis (87). Because of inactivation by alveolar surfactant, daptomycin is not effective in the treatment of pneumonia. However, it has excellent concentrations in all other tissues (88–90).

Mechanism of Action, Pharmacology, Administration, and Dosage

Daptomycin works by binding to and interfering with the integrity of cell wall structure in gram-positive bacteria but does not penetrate the bacterial cytoplasm. Upon binding, transmembrane channels are formed, causing rapid depolarization of membrane potential and inhibition of protein, DNA, and RNA synthesis, resulting in bacterial cell death. It has a concentration-dependent bactericidal activity.

Daptomycin is poorly absorbed orally and should be administered intravenously only. Direct toxicity to muscles prohibits intramuscular injection. Daptomycin is highly bound to human plasma protein (92%), primarily to serum albumin. The serum half-life is eight to nine hours in normal subjects, allowing once daily administration. Approximately 80% of the administered drug is excreted unchanged by the kidney with a smaller portion (6%) excreted in the feces. Dosage adjustment is required for creatinine clearance below 30 mL/min. Daptomycin is removed by hemodialysis and the dose should be administered immediately following dialysis.

Antimicrobial Activity/Spectrum/Resistance

Daptomycin is unable to permeate the outer membrane of gram-negative bacteria, thus its spectrum of activity is limited to gram-positive organisms only. Daptomycin is active in vitro against both antibiotic-susceptible and resistant gram-positive bacteria, including Staphylococci (MSSA, MRSA, VISA, and VRSA), *S. pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equismilis*, and Enterococci (both *E. faecalis*, and *E. faecium* including (VRE), and *S. pneumoniae* (including penicillin-resistant).

In an in vitro comparative study with vancomycin, linezolid, and quinupristin/dalfopristin, daptomycin was found to have the most rapid bactericidal activity and

approximately 8- to 30-fold greater activity against MSSA and MRSA than the other products (90,91). Against VISA, quinupristin/dalfopristin was the most active agent, followed by daptomycin, linezolid, and vancomycin (92). The activity of daptomycin against both VRE vancomycin-sensitive *E. faecalis* was greater than all the other agents tested (92,93).

Bacteria in the stationary growth phase (as occurs in endocarditis and foreign body infections) are killed faster with daptomycin than with vancomycin or nafcillin. To date, no mechanism of resistance to daptomycin or cross-resistance with other antimicrobials has been reported.

Adverse Effects and Drug Interactions

The most frequently reported side effects with daptomycin use are headache, constipation, and rash. Initial development of daptomycin was suspended in the early 1980s due to concerns of skeletal muscle toxicity. With less frequent administration (98 hour vs. daily), clinical toxicity has not been seen. Elevations in serum creatine phosphokinase (CPK) have been reported in patients receiving daptomycin. Accordingly, weekly CPK levels should be monitored, and patients should be examined for muscle pain or weakness throughout therapy. Daptomycin should be used cautiously in patients with a history of myopathy or peripheral neuropathy. Although no drug-drug interactions have been identified, patients receiving medications that have the potential to cause rhabdomyolysis, such as HMG-CoA reductase inhibitors, should be closely monitored during daptomycin use. Daptomycin does not inhibit or induce the C-P450 enzymes.

Therapeutic/Clinical Uses

Daptomycin is indicated for treatment of complicated skin and skin structure infections caused by MSSA and MRSA, VISA, and VRSA strains, hemolytic streptococci, and vancomycin-susceptible enterococci and VRE. A recent clinical trial demonstrated that daptomycin is noninferior to comparator agents (vancomycin and semi-synthetic penicillins) for the treatment of bacteremia and right-sided endocarditis due to *Staphylococcus aureus*; The drug recently received FDA approval for these indications. Daptomycin is uniquely ineffective for the treatment of pneumonia due to its inactivation by surfactant, and is not appropriate for this infection.

SULFONAMIDES AND TRIMETHOPRIM

History/Description

Sulfonamides are derived from sulfonic acid, and were discovered in 1932. Sulfamethoxazole (SMX) and Sulfadiazine remain the most useful members of this class of antibiotics. Trimethoprim (TMP) was first used for the treatment of infections in humans in 1962, and it was registered for clinical use in combination with SMX in 1968 (94,95).

Mechanism of Action, Pharmacology, Administration, and Dosage

TMP and SMX in combination have synergistic effects. The optimal ratio of serum concentrations of TMP to SMX against most bacteria is 1:20. Both drugs inhibit bacterial folic acid synthesis at different steps in the pathway. SMX inhibits dihydropteroate synthetase, which catalyzes the formation of dihydrofolate from para-aminobenzoic acid. In the subsequent step of the pathway, TMP inhibits

dihydrofolate reductase, which catalyzes the formation of tetrahydrofolate from dihydrofolate.

TMP is 45% and SMX is 66% bound to plasma proteins. In patients with normal renal function, the half-lives of TMP and SMX are approximately 11 and 9 hours, respectively. When the creatinine clearance decreases to less than 30 mL/min, the dosage of TMP/SMX should be adjusted.

TMP/SMX (trade names Bactrim[®] or Septra[®]) is available in a single strength tablet, containing 80 mg TMP and 400 mg of sulfamethoxazole; a double strength tablet, containing 160 mg TMP and 800 mg of sulfamethoxazole; as an oral suspension; and intravenous solution. Dosing equivalents for TMP/SMX are one DS tablet equivalent to 10 mL intravenous solution, equivalent to 20 mL oral suspension. For most indications, one double-strength tablet is administered twice daily for 7 to 14 days depending on the type and severity of the infection. For the treatment of *Pneumocystis carinii* pneumonia (PCP) the administration of dosages of 15 mg/kg of TMP daily, is recommended typically divided into three doses for 21 days. PCP prophylaxis may be achieved with 1 double-strength tablet daily or every other day.

Antimicrobial Activity/Spectrum/Resistance

Many aerobic gram-positive and gram-negative bacteria, *Pneumocystis carinii*, and several protozoa are inhibited or killed by clinically achievable concentrations of TMP/SMX. Certain nosocomial pathogens, such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Serratia* spp. are frequently susceptible to SMZ-TMP. In immunosuppressed individuals, some microorganisms of particular concern such as *Nocardia asteroides* and *Listeria monocytogenes* are also usually inhibited by TMP/SMX.

Important pathogens that are usually resistant to TMP/SMX are *P. aeruginosa*, *B. fragilis*, and most other obligatory anaerobic bacteria. Additionally, *M. tuberculosis*, *Campylobacter* spp., *Treponema pallidum*, and *Rickettsiae* are resistant to SMZ-TMP. MRSA is variably susceptible, and most penicillin-resistant pneumococci are resistant. The clinical use of TMP/SMX has gradually declined during recent decades as a result of growing resistance to this agent among most major bacterial pathogens (96).

Adverse Effects and Drug Interactions

SMX can cause blood dyscrasias. Hypersensitivity reactions may also occur with this medication, most commonly manifested as rashes, but may include erythema multiforme major (Stevens-Johnson syndrome). TMP has fewer life-threatening side effects than do the sulfonamides. However, TMP has been shown to cause drug-induced aseptic meningitis. TMP/SMX is contraindicated in pregnancy. TMP/SMX may potentiate the effects of warfarin, phenytoin, tolbutamide, and chlorpropamide.

Therapeutic/Clinical Uses

Growing resistance and potential toxicity has led to the decreased use of TMP/SMX. However, this agent is still used in the treatment and prophylaxis of urinary tract infections, treatment and prevention of PCP, shigellosis, and otitis media. Of note, TMP/SMX is being used more frequently in the treatment of severe Staphylococcal infections (97). **✓ TMP/SMX may be extremely useful in severe infections caused by susceptible organisms in the critically ill patient, especially those infections caused by *Enterobacter***

sp., and other gram-negative rods that may be multi-resistant to beta-lactam drugs. ⚡

QUINOLONES

History/Description

Nalidixic acid, the first quinolone, was developed in 1962 as a byproduct of chloroquine synthesis, and was only useful in urinary tract infections. Its poor pharmacokinetic profile and its toxicity led to the development of the 6-fluorine-substituted quinolones in the 1980s. The fluoroquinolones are reviewed in references (98–100).

Mechanism of Action, Pharmacology, Administration, and Dosage

The quinolones have a novel mechanism of action. These compounds target bacterial topoisomerases II and IV. Topoisomerase II (also known as DNA gyrase) is responsible for nicking and sealing DNA, as well as regulating supercoiling. Topoisomerase IV separates the DNA daughter molecules after DNA replication.

The quinolones have excellent oral bioavailability (approximately 90–99%), which allows for early conversion from intravenous to oral formulations. All are available as tablets or capsules. Parenteral formulations of ciprofloxacin, gatifloxacin, ofloxacin, levofloxacin, moxifloxacin, and trovafloxacin (as the pro-drug alatrofloxacin) are also available. Administering the fluoroquinolones with food delays the absorption, but does not alter its extent. However, concomitant administration of divalent ions such as aluminum, magnesium, zinc, iron, and/or calcium may block absorption.

The quinolones have a post-antibiotic effect of approximately one to two hours, similar to the aminoglycosides, but greater than that with the beta-lactam antibiotics (101). Gemifloxacin and trovafloxacin have a greater tendency to bind to proteins than the other quinolones

(approximately 70% vs. less than 50% for the other quinolones), but are not likely to displace other protein-bound drugs.

Routes of metabolism vary greatly between the different quinolones. Moxifloxacin and trovafloxacin undergo extensive hepatic metabolism; however, the metabolites are less active than the parent compounds. Ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, and ofloxacin are renally eliminated. The fluoroquinolones have elimination half-lives of approximately 3 to 20 hours. Please refer to Table 10 for dosing of the commercially available quinolones.

Antimicrobial Activity/Spectrum/Resistance

⚡ Quinolone antibiotics, similar to the cephalosporins, are traditionally categorized into first to fourth generations based upon spectrum of activity. In general, the second, third, and fourth generations have enhanced gram-positive cocci activity (except ciprofloxacin) and gram-negative rod activity. Excellent anaerobic activity is seen with trovafloxacin and moxifloxacin. ⚡

In 1995, an alarming trend toward increased resistance to ciprofloxacin was noted in *S. aureus*, *E. coli*, *Citrobacter freundii*, *S. marcescens*, and *P. aeruginosa*. The activity of the fluoroquinolones against gram-positive bacteria has been reviewed (102). Approximately 28% of the fluoroquinolone-resistant enteric bacilli also demonstrated aminoglycoside and B-lactam resistance. Multiple mechanisms, many of which are bacteria-specific have been identified in fluoroquinolone resistance, and different bacteria may acquire more than one mutation to confer resistance. Because mutations in the genes that code for the subunits of topoisomerase II and IV vary between bacteria, patterns of quinolone resistance will vary.

Adverse Effects, Drug Interactions

About 5% of patients experience GI side effects with the fluoroquinolones (100). CNS effects (headache, dizziness, insomnia, and nervousness) are also noted with some of

Table 10 Quinolones: Dosing

Quinolone	Dosage form	Dose (mg)	Dosing interval (hours)	Adjust dose (for renal impairment)	Dosage adjustment
<i>First generation</i>					
Nalidixic acid	PO	250, 500, 1000	6	None	None
<i>Second generation</i>					
Ciprofloxacin	PO	250, 500, 750	8, 12	CrCl <30 mL/min, HD ^a	250–500 mg q18 hr 250–500 mg q24 hr, after HD ^a
	IV	200, 400	8, 12	CrCl <30 mL/min	200–400 mg q18–24 hr
<i>Third generation</i>					
Levofloxacin	PO	500, 750	24	CrCl 20–50 mL/min	500–750 mg LD, then 250–500 mg q24 hr
	IV	500, 750	24	CrCl <20 mL/min	500–750 mg LD, then 250–500 mg q48 hr
<i>Fourth generation</i>					
Trovafoxacin ^a	PO	200	24	Hepatic	Avoid if possible, if not, half-dose
	IV	300	24	Impairment	
Moxifloxacin	PO	400	24	Hepatic	Not studied
	IV	400	24	Impairment	
Gemifloxacin	PO	320	24	CrCl <40 mL/min	320 mg LD, then 160 mg qd

^aTrovafoxacin should only be used in hospitalized patients when the potential benefits are greater than the risks. See text.

Abbreviations: HD, hemodialysis; IV, intravenously; LD, loading dose; PO, per OS.

the quinolones, primarily at higher dosages. Allergic reactions occur in 1% to 2% of patients. Phototoxicity is a possible side effect with fluoroquinolone therapy. Although taking the medication at bedtime can reduce this effect, patients should remain indoors and away from ambient light while on this drug.

Maintaining adequate hydration and urine acidity will prevent crystalluria, an infrequent effect of the fluoroquinolones. Laboratory test abnormalities, including hematologic, hepatic, and renal function markers, occur at a rate of approximately 11.6%. Both hypoglycemia and hyperglycemia have been reported with all the quinolones.

Animal studies have shown that the fluoroquinolones have a propensity to cause toxicity to chondrocytes (103). Tendon rupture has also been described with many of the fluoroquinolones (104–116). Recent research indicates that oxidative stress is involved (103). There is an increased risk in the elderly, those on steroids, and those with renal failure (105). For this reason, fluoroquinolones should be avoided in the elderly when other options exist; and those who must take a fluoroquinolone should be advised to avoid heavy exercise. If a patient complains of tendon pain, fluoroquinolones should be discontinued unless there are very compelling indications for their use. Additionally, fluoroquinolones should not be prescribed for pregnant and breast-feeding women, and only used for specific indications for children. Trovafloxacin has also been found to cause rare but fatal cases of liver toxicity. Therefore the FDA has asked that it be reserved for short-term intravenous use for life-threatening infections in hospitalized patients.

In contrast to ciprofloxacin, the third- and fourth-generation quinolones do not seem to inhibit theophylline or caffeine metabolism. Although a modest increase in digoxin concentrations was noted in studies with gatifloxacin, no change in the renal elimination of digoxin was noted, therefore no dosage adjustments appear necessary for either drug (117).

QT_c prolongation has been reported at a rate of less than 1% for nearly all the quinolones, but the manufacturer reports an incidence 1.3% for sparfloxacin. Torsades de pointes have been reported with all quinolones but seem to occur more frequently with levofloxacin, gatifloxacin, sparfloxacin, and moxifloxacin. The potential for QT_c prolongation with sparfloxacin and moxifloxacin suggests concomitant Class IA and Class III anti-dysrhythmic drugs should be avoided (Volume 2, Chapter 20). Case reports with ciprofloxacin had noted increased levels of cyclosporine and decreased levels of phenytoin. Levels of these medications should be carefully monitored with ciprofloxacin administration.

Therapeutic/Clinical Uses

All of the newer quinolones offer lower MICs against various streptococcal species, particularly *S. pneumoniae* although there are reports of *S. pneumoniae* resistance to levofloxacin (118). Compared with the newer entities, ciprofloxacin retains equal or better activity against enteric gram-negative rods (especially *P. aeruginosa*). As a result of their anaerobic activity, several of the fluoroquinolones may be useful in the treatment of both community-acquired and hospital-acquired aspiration pneumonia (119), although older agents of different classes still remain useful with more clinical experience. Trovafloxacin, gatifloxacin, and moxifloxacin have enhanced in vitro activity against anaerobes, a property not demonstrated by previous fluoroquinolones. Resistance

in anaerobic bacteria, most importantly of the *B. fragilis* group, is increasingly common. The newer agents appear to also have activity against atypical bacteria, such as *Legionella* spp. and *Mycoplasma pneumoniae*. The fluoroquinolones, especially moxifloxacin, gatifloxacin, and levofloxacin (in this order) are sometimes useful in the treatment of mycobacterial infections (120).

TOPICAL ANTIMICROBIALS FOR BURN WOUNDS

General Considerations

Burns impair the skin integrity, allowing infectious organisms to invade deeper tissues. Within hours of sustaining a burn, gram-positive organisms populate the wound. After several days, more virulent gram-negative organisms replace the gram-positive ones. The most commonly isolated gram-negative organisms include *P. aeruginosa*, *Proteus* spp., and *Klebsiella* spp (121). The gram-negative organisms have greater morbidity, possess many antibiotic resistance mechanisms, and have the ability to secrete collagenases, proteases, lipases, and elastases, enabling them to proliferate and penetrate into the subeschar space (122). If host defenses are inadequate, invasion of viable tissue occurs. Please refer to Volume 1, Chapter 34 and the following references for additional information about topical antimicrobials and burns (123–127).

Topical antimicrobials are applied after injury to limit bacterial colonization. Established infection requires use of topical agents that can penetrate the eschar to reduce microbial counts and to prevent systemic dissemination. Systemic agents are instituted for cellulitic wound infections, gram-positive suppurative infections, extensive fungal invasion, or systemic spread.

Mafenide (Sulfamylon)

Mafenide was discovered by German scientists just before World War II but was not used clinically until the early 1960s after Robert Lindberg demonstrated its ability to control *P. aeruginosa* infections in a rat-burn model.

Mafenide is a topical sulfonamide formulated as an 11.1% suspension in a water-soluble cream base. It diffuses rapidly and freely into the eschar, and is detected in the systemic circulation. Mafenide is renally metabolized to an inactive salt. The salt itself constitutes a large osmotic load, promoting an osmotic diuresis. Mafenide is also metabolized to a carbonic anhydrase inhibitor that may result in a clinically significant metabolic acidosis.

Mafenide should be avoided in patients with renal impairment. Occlusive dressings should not be used, as the drug is usually applied every 12 hours, but it dissipates from the wound surface after approximately three hours (due to its excellent absorption), leaving up to nine hours of bacterial proliferation time on the wound surface. However, tissue levels remain adequate for 9 to 10 hours after application.

Mafenide has excellent bacteriostatic activity against most gram-positive species, including clostridia, but has limited activity against some *S. aureus*, particularly methicillin resistant strains. Mafenide is highly effective against gram-negative organisms, including *Pseudomonas* spp., but has minimal antifungal activity.

Pain or burning frequently occurs upon application to partial thickness burns. The pain is hypothesized to result from the hyperosmotic properties of the preparation, as well as some irritating quality of the drug itself. Hypersensitivity reactions may also occur in up to 50% of patients

treated with this agent (124), and rashes may mimic cellulitis (127).

Mafenide may still be the most useful agent for the treatment of invasive burns because of its superior eschar penetration, but careful monitoring of pulmonary function and acid-base status is critical.

Silver Nitrate

Silver nitrate solutions had been used for centuries as an incompletely understood antiseptic. In 1965, Moyer (128) reintroduced topical use of silver nitrate to burn wound management where it is typically employed as a 0.5% solution. The precise mechanism of action is unknown, but ionic silver is known to exert bacteriostatic activity via several potential mechanisms.

Silver nitrate does not penetrate the burn eschar because silver chloride and other silver salts are highly insoluble and precipitate on the wound surface. Application with silver nitrate is relatively painless, but requires frequent nursing attention, as the dressing cannot be allowed to dry. The dressing must be rewetted every two to three hours with fresh 0.5% silver nitrate solution, otherwise the concentration of silver nitrate rises to caustic levels.

Silver nitrate is effective against most strains of *S. aureus* and coagulase-negative Staphylococci, and it also has activity against *P. aeruginosa*. It has less activity against other gram-negative species such as *Enterobacter* spp. and *Klebsiella* spp. An advantage of this compound is the infrequent emergence of silver-resistant bacteria.

Silver nitrate's insolubility requires it be prepared with distilled water. This results in a hypotonic compound. This hypotonicity causes electrolyte abnormalities as the silver removes electrolytes from the wound. Hyponatremia is the most common electrolyte disturbance. Hyponatremia can become significant, even fatal, when children with large burns are treated for long periods with silver nitrate and do not have their serum sodium monitored or replaced. Silver nitrate also stains everything it comes into contact with brown-black. Methemoglobinemia can occur with silver nitrate but is a rare complication, related to bacterial oxidation of nitrate to nitrite. The organism most often involved when patients have developed methemoglobinemia is, *Enterobacter cloacae*, as this organism efficiently metabolizes nitrate (NO_3^-) to nitrite (NO_2^-) and in so doing oxidizes the iron heme moiety hemoglobin from ferrous (Fe^{++}) to ferric (Fe^{+++}).

The vigilant nursing attention required with this compound, coupled with the fact that silver nitrate does not penetrate the eschar, means this compound should be avoided in very deep burns or in wounds where topical care has been delayed and the wounds are already heavily colonized. However, silver nitrate is attended with rapid debridement of the eschar, and less hypertrophic scar is seen than with other compounds.

Silver Sulfadiazine (Silvadene)

Silver sulfadiazine (SSD) was formulated in 1967 by mixing the weakly acidic sulfadiazine with silver nitrate. It was initially thought that both the silver ion and sulfadiazine had antimicrobial properties; however more recent work suggests sulfadiazine is simply an effective means of delivering silver to the wound. Penetration of SSD into the wound is intermediate between the readily absorbed mafenide and minimally absorbed silver nitrate. Unlike mafenide, the application of SSD is painless. Its antibacterial activity

lasts up to 24 hours, but like most burn agents, it is often applied every 12 hours coupled with daily wound debridement.

SSD has bactericidal activity against many gram-positive and gram-negative bacteria, as well as yeast. SSD has excellent activity against *P. aeruginosa* and *S. aureus*. Generally, more organisms are resistant to SSD than mafenide. And although SSD-resistant strains of *P. aeruginosa* and enteric gram-negative rods have been reported, the incidence of infection with these resistant organisms is not increasing.

SSD is contraindicated for pregnant or breast feeding women because of the possibility of kernicterus in the infant. SSD should also be used with caution in patients with G6PD deficiency and renal insufficiency. This compound may induce leukopenia as a result of direct bone marrow suppression, but this generally resolves over 72 to 96 hours without discontinuing the medication with no concomitant increase in morbidity or mortality in studies. Hypersensitivity reactions are relatively uncommon with cutaneous reactions occurring in fewer than 5% of patients (124). SSD may cause sulfa crystal formation in the urine, but this is less of a problem when patients are adequately hydrated. Absorption of propylene glycol (the vehicle) has also been reported to cause problems in evaluating the patient's serum osmolality, as this causes an osmolar load. The effect of proteolytic enzymes (collagenase, papain, suti-lains) is reduced when used concomitantly with SSD. ⚡ **SSD represents a compromise between the high efficacy of mafenide and the high maintenance of silver nitrate. It is therefore the most commonly employed topical antimicrobial agent in the burn patient, and frequently used as combination treatment (often alternating every 12 hours) with mafenide.** ⚡

ANTI-MYCOBACTERIAL AGENTS

General

⚡ Although many anti-TB agents are available, the most important drugs for therapy of critically ill patients are commonly known as "RIPE" which stands for: rifampin, isoniazid, pyrazinamide, and ethambutol (49,50). ⚡ Certain other antituberculosis agents also have an important role and include streptomycin and certain fluoroquinolone antibiotics (129,130). Linezolid also has antimycobacterial activity, but its expense precludes its frequent use. The first two agents of RIPE, namely, rifampin and isoniazid, a few of the fluoroquinolone antibiotics, and numerous aminoglycoside agents are available for parenteral administration. With the recent epidemic spread of TB in the United States and worldwide (131) and the fear of multi-drug resistant TB, critical care clinicians are likely to use these drugs with increasing frequency. The "gold standard" recommendations for the treatment of TB infections emanate from the American Thoracic Society and the Centers for Disease Control and Prevention (132–134).

Treatment Recommendations

Treatment recommendations typically include isoniazid (INH), rifampin, pyrazinamide, and ethambutol (Table 11).

INH is the hydrazine of isonicotinic acid, and is bactericidal against replicating mycobacteria (including *M. tuberculosis*, and some atypical mycobacteria). It appears to work by inhibiting mycolic acid formation in the cell wall.

Table 11 First-Line Anti-TB Medications, Dosage, and Adjustment for Renal and Hepatic Insufficiency

Anti-TB drug name	Dosage form	Standard dose	Dosing interval	Requires dose adjustment for renal insufficiency (CrCl <30 mL/min)	Requires dose adjustment for hepatic failure
INH	PO or IM	300 mg (5 mg/kg)	Every 24 hr	No	Yes
RIF	PO or IV	600 mg (10 mg/kg)	Every 24 hr	No	Yes
RFB	PO	300 mg (5 mg/kg)	Every 24 hr	No	Yes
PZA	PO	2000 mg (25 mg/kg)	Every 24 hr	Yes	Yes
EMB	PO	1000 mg (15–25 mg/kg)	Every 24 hr	Yes	No
SM	IM or IV	1000 mg (12–15 mg/kg)	Every 24 hr	Yes	No

Abbreviations: EMB, ethambutol; IM, intramuscular; INH, isoniazid; IV, intravenously; PO, per OS; PZA, pyrazinamide; RIF, rifampin; RFB, rifabutin; SM, streptomycin.

Approximately one in 10⁵ TB organisms is genetically resistant (intrinsic resistance) to INH.

INH is well absorbed enterally, and therapeutic levels are obtained in all body tissues, including the CSF. The drug is acetylated and hydrolyzed and then excreted in the urine. Acetylation is genetically determined, and INH serum concentration is 50% to 80% lower in rapid acetylators than in slow acetylators.

INH-induced side effects develop in approximately 5% of patients and may include rash, peripheral neuritis, fever, hypersensitivity reactions (including an SLE-type reaction), and jaundice arthritis. Peripheral neuritis can be prevented with concurrent administration of pyridoxine (vitamin B₆). Hepatic injury due to INH is the most common concern with its use. A mild increase in hepatic transaminases (ALT and AST two to three times the upper limit of normal) is common and does not predict more serious hepatic injury. The drug need not be stopped in these patients as long as they are monitored. In contrast, the drug should be discontinued immediately in patients with symptoms of hepatitis (nausea, malaise, anorexia, and jaundice) including those whose transaminases are above five times normal. The risk of hepatitis is increased in people who drink large quantities of alcohol and in patients with chronic hepatitis from other causes. Older patients are also at higher risk for both neuritis and hepatic damage, but isoniazid should not be withheld in the elderly if they have recent skin test conversion or active TB despite the hepatitis risk.

Rifampin is just as potent as isoniazid for TB. Rifampin is also active against many gram-positive and gram-negative organisms in addition to *M. tuberculosis* by inhibiting the bacterial DNA-dependent RNA polymerase, which suppresses the initiation of RNA chain synthesis. A single point mutation in the target enzyme is sufficient to confer resistance, and resistance occurs quickly when it is used as a single agent, therefore, the drug must be combined with other antibiotics.

Rifampin is well absorbed orally and distributes widely in body tissues, including the CSF. Rifampin is metabolized in the liver by active deacetylation and is ultimately excreted via the bile in the gastrointestinal tract. Adverse effects due to rifampin occur in about 4% of patients and include fever, rash, jaundice, GI upset, and hypersensitivity reactions.

Rifampin increases the metabolism of numerous drugs, including some B-blockers, corticosteroids, oral contraceptives, warfarin, some oral hypoglycemics, some antiarrhythmics, various immunosuppressants (cyclosporine,

tacrolimus, sirolimus), clarithromycin, triazole antifungals, protease inhibitors, methadone, theophylline, and phenytoin (135). Reduced drug levels may cause serious problems unless the affected drug dose is appropriately adjusted. Conversely, caution must be exercised when discontinuing rifampin therapy to avoid supratherapeutic and/or toxic effects. Rifabutin can be used as an alternative to rifampin. It can be given less frequently and has fewer drug interactions than rifampin.

Rifaximin, an analog of rifampin, was recently approved by the FDA for traveler's diarrhea. Of note, it is devoid of *M. tuberculosis* activity. In the ICU, rifaximin (400 mg orally three times daily) has been used enterally in place of neomycin for hepatic encephalopathy (134). Both neomycin and rifaximin are minimally absorbed enterally, and both inhibit the urease-producing bacteria responsible for intestinal ammonia production. Neomycin can cause ototoxic and nephrotoxic effects, especially if used over several months. Rifaximin is not approved in the US for this indication; however, it is increasingly employed to protect against hepatic encephalopathy because it is not associated with either renal toxicity or ototoxicity (136).

Pyrazinamide is an analog of nicotinamide and is well absorbed orally, and penetrates tissues throughout the body (129). Pyrazinamide is a pro-drug and is metabolized to pyranizic acid, which is bactericidal against intracellular replicating organisms. The exact mechanism of action is unknown; pyrazinamide is hydrolyzed by the liver and is excreted primarily by renal glomerular filtration. Hepatotoxicity is the most common side effect and has been reported in approximately 15% of patients who received 40 to 50 mg/kg/day, a regimen used previously. With current dosages of 15 to 30 mg/kg/day, pyrazinamide toxicity is substantially lessened. The drug can also cause hepatitis, arthralgias, and nausea.

Ethambutol is an orally active compound with excellent tuberculostatic activity. The drug widely distributes throughout the body, including the CSF. Approximately 50% of the dose is excreted unchanged in the urine. Optic neuritis occurs rarely with the standard dose of 15 mg/kg/day. Patients should be tested for visual acuity and green color perception before and periodically during ethambutol therapy. If a dosage of more than 15 mg/kg/day adjusted for renal function is used, tests should be conducted monthly. Other adverse effects are rare.

Streptomycin is an aminoglycoside antibiotic long used to treat tuberculosis, and is tuberculocidal. Vestibular toxicity, auditory toxicity, and to a lesser degree than the

Table 12 Clinically Significant Fungi and Their Antimicrobial Drugs of Choice

Microorganism	Drug of choice ^a	Alternative agents
<i>Aspergillus</i> sp.	Voriconazole	Itraconazole, amphotericin B, an echinocandin ^b
<i>Candida</i> sp.	An echinocandin ^b	Fluconazole, voriconazole, amphotericin B
<i>Coccidioides immitis</i>	Amphotericin B	Fluconazole, itraconazole, voriconazole, posaconazole?
<i>Cryptococcus neoformans</i>	Amphotericin B plus flucytosine	Fluconazole plus flucytosine
<i>Histoplasma capsulatum</i>	Amphotericin B	Itraconazole, voriconazole
<i>Mucor-Absidia-Rhizopus</i> (Zygomycetes)	Amphotericin B	Posaconazole?

^aAmphotericin lipid formulations are less toxic.

^bAn echinocandin = anidulafungin, caspofungin, micafungin.

other aminoglycosides, nephrotoxicity has been reported with streptomycin use. Amikacin is sometimes used in place of streptomycin to treat tuberculosis.

Various fluoroquinolones, namely, moxifloxacin, gatifloxacin, and levofloxacin, have been used as second line therapy in the treatment of tuberculosis in combination with other antituberculosis agents, but their efficacy for the treatment of tuberculosis is not entirely clear (101).

ANTIFUNGALS

History/Description

Introduced in 1960. Amphotericin B was the first clinically useful anti-fungal agent for the treatment of systemic fungal infections. Subsequently, lipid-based preparations of amphotericin B (with diminished toxicities) has made therapy safer. Additionally, the introduction of agents with different mechanisms of action (i.e., 5-flucytosine, miconazole, voriconazole, and the echinocandins), have increased the ability to treat serious fungal infections (137–140). The major fungi responsible for human disease and their antifungal drugs are summarized in Table 12.

Mechanism of Action, Pharmacology, Administration, and Dosage

Amphotericin B and all of the lipid-based preparations bind to ergosterol, an essential component of the fungal cell wall, with the resultant membrane permeability leading to cell death. Nystatin is in the same class of antifungal drugs as amphotericin but is not given systemically and is used

primarily topically (e.g., swish and swallow) and for oral and esophageal candidiasis. Table 13 shows the characteristics of various amphotericin B formulations. Liposomal amphotericin B is better tolerated than other formulations of amphotericin B (141). The azoles, including the triazoles, inhibit the fungal cytochrome P450 enzymes responsible for the conversion of lanosterol to ergosterol, an essential compound for fungal replication and the target upon which amphotericin acts. Table 14 compares the various azole agents. Refer to Tables 13 and 14 for dosing guidelines of the various preparations of amphotericin and the azoles, respectively.

Caspofungin, the first licensed drug in the class of echinocandins, inhibits cell wall synthesis by acting upon the beta-1,3 glucan synthase (142). Some fungi have cell wall glucans, which are glucose polymers akin to cellulose in plant cell walls; other fungi have chitin, which is a polymer of glucosamine. Echinocandins are not active against fungi that have chitin in the cell wall; this property restricts the range of fungi that can be targets for this class of drug.

Caspofungin, only available in a parenteral formulation, is given as a loading dose of 70 mg/kg, followed by 50 mg per day with dose adjustment for hepatic insufficiency. Caspofungin can cause some hepatic toxicity with elevation of liver enzymes and bilirubin. There is no dosage adjustment for renal insufficiency; safety data shows that it can be used in patients with mild to moderate hepatic disease (Child-Pugh class B), but its safety in patients with severe liver disease is untested (143). The FDA approved a second echinocandin drug, micafungin, for the

Table 13 Characteristics of Various Amphotericin Formulation Preparations

Characteristic	Amphotericin B deoxycholate	Amphotericin B cholesteryl sulfate	Amphotericin B lipid complex	Liposomal Amphotericin B
Brand name	Fungizone [®]	Amphotec [®]	Abelcet [®]	AmBisome [®]
Chemical composition	Micelle	Lipid disks	Ribbons and sheets	Liposomes
Relative infusion-related toxicity	++++	++	++	+
Relative nephrotoxicity	++++	+	+	+
Dosage (mg/kg/day)	0.5–1	3–4	5	3–5

Note: Relative infusion-related toxicity and relative nephrotoxicity are in comparison with amphotericin B deoxycholate, and range from + (mild) to ++++ (severe).

Table 14 Major Pharmacologic Properties of Azole Antifungals

Factor	Ketoconazole	Fluconazole	Itraconazole	Voriconazole
Brand name	Nizoral [®]	Diffucan [®]	Sporanox [®]	Vfend [®]
Oral absorption decreased by H ₂ -blocking agent or antacid	Yes	No	Capsule—yes: suspension—no	No
Half-life (hours)	9	25	15–42	6
Clearance	Hepatic	Renal	Hepatic	Hepatic
Urinary levels of active drug	Low	High	Low	Low
Penetration of CSF ^a	Poor	Excellent	Poor	Unknown
Typical dose	200 mg PO q12 hr	400 mg PO/IV q24 hr	200 mg PO/IV q12 hr	200 mg PO/IV q12 hr

^aPenetration into CSF does not always correlate with clinical efficacy in meningitis.

Abbreviations: CSF, cerebrospinal fluid; IV, intravenously; PO, per OS.

use in treating esophageal candidiasis and febrile neutropenia in recipients of hematologic stem cell transplants. It has not received approval yet for invasive candidiasis or invasive aspergillosis. However, its mechanism of action and its in vitro spectrum of activity are identical to those of caspofungin, so it will probably be used for these purposes (144). Another echinocandin, anidulafungin, anidulafungin, the third FDA approved echinocandin; it has the same spectrum of activity and mechanism of action as caspofungin (145). Neither micafungin or anidulafungin requires dose adjustments for end stage renal disease or end stage liver disease, including Child-Pugh "Class C" disease.

Flucytosine inhibits the formation of fungal RNA and DNA. Inside fungal cells, 5-FC is converted to 5-fluorouracil, which interferes with pyrimidine metabolism and decreases the pool of precursors for incorporation into DNA and RNA, thereby inhibiting DNA replication and fungal cell multiplication. 5-FC is readily bioavailable when given orally. It distributes widely to body tissues, including the central nervous system. It is not metabolized by humans and is excreted unchanged in the urine, so it must be used cautiously in patients with renal insufficiency. Levels must be monitored so that steady state levels are from 25 to 100 mcg/mL to avoid toxicity.

Antimicrobial Activity/Spectrum/Resistance

Amphotericin B remains the reference standard by which all anti-fungal agents are measured because it has the broadest spectrum, and has been available for the longest period of time. Amphotericin B has activity against most fungi and yeasts; however, several organisms that are not usually pathogens in the ICU display intrinsic resistance, including *Cladosporium* spp. and *Fonsecaea* spp., and it has variable activity against *Fusarium* spp., *Scedosporium* spp. and *Sporothrix schenckii*. Alternative anti-fungals for these organisms include voriconazole in most cases, or sometimes flucytosine (which should not be used as a single agent). Because of these resistance patterns in these relatively unusual molds, it is increasingly important that complete identification of clinically important fungi and yeasts be performed. Some *Candida albicans* have developed resistance to fluconazole, some have unpredictable resistance patterns (*C. glabrata*), and certain non-albicans *Candida* are intrinsically resistant to the fluconazole (such as *C. krusei*).

Itraconazole is effective against *Candida* spp. Additionally, it has activity against *Aspergillus* spp. and some of the organisms that cause endemic mycoses, such as *Coccidioides immitis* and *Histoplasma capsulatum*. Its major drawback is poor bioavailability; the capsules do not dissolve in the

absence of gastric acid, and the drug is poorly absorbed. The suspension is well-absorbed, but it is unpalatable.

Voriconazole is effective against most strains of fluconazole-resistant *C. albicans* and *C. glabrata*. In contrast to the other azoles, it is fungicidal for *Aspergillus*, *Scedosporium*, and *Fusarium*, although it has poor activity against Zygomycetes (which includes mucor), where amphotericin B remains the drug of choice (146). The efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis was recently reviewed by Denning et al. (147) Voriconazole was recently shown to have better responses and improved survival against invasive aspergillosis, and have fewer severe side effects than the standard therapy of amphotericin B (148). In addition, an oral formulation of voriconazole is available with excellent oral bioavailability, making itraconazole and voriconazole the only oral agents with activity against *Aspergillus* sp.

Posaconazole is a new triazole drug that has received FDA approval for treatment of candida infections and for prophylaxis of invasive fungal infections, specifically in the setting of cancer chemotherapy and transplantation (149). Posaconazole is promising because it has activity against the zygomycetes, which are the cause of invasive mucormycosis (150). One potential disadvantage to the use of posaconazole is that there is no intravenous formulation. It does come as a suspension and may be given orally or down a nasogastric tube. Ravuconazole is another triazole in phase III testing (151). It also has activity against *Candida* and *Aspergillus*; it is not as active against zygomycetes as posaconazole. They both may be useful for treating fungi that are resistant to some of the older azole drugs.

Caspofungin is only clinically effective for infections due to *Aspergillus* spp. and *Candida* spp. Caspofungin has been shown to be at least as effective as amphotericin B for the treatment of invasive candidiasis, and candidemia (152). It is also as effective as liposomal amphotericin in the treatment of aspergillosis and has fewer side effects. Caspofungin is not active against *Cryptococcus* spp. (142,143), despite the fact that this organism has a polyglucan cell wall; the large capsule that surrounds the *Cryptococcus* sterically prevents the drug from reaching its site of action.

Adverse Effects and Drug Interactions

Amphotericin

Amphotericin B has immediate (infusion-related toxicities) and delayed nephrotoxic effects. Infusion-related toxicities include fever, chills, rigors, myalgia, malaise, nausea, and vomiting. Pre-medication with acetaminophen, diphenhydramine, and low-dose meperidine (for rigors) may mitigate

these responses. Hypotension, bradycardia, and ventricular dysrhythmias may also occur and are related to the infusion rate of amphotericin. All of the amphotericin preparations can cause these infusion-related adverse effects; however, they tend to be less frequent and less severe with the lipid preparations than with the deoxycholate formulation (140). The major delayed adverse effects of amphotericin B involve the kidney, and these can become permanent. These effects include nephrotoxicity, electrolyte abnormalities (especially hypokalemia and hypomagnesemia), and renal tubular acidosis. Amphotericin B deoxycholate is more nephrotoxic than the other lipid-based preparations of amphotericin B; however, these other agents still exhibit dose and time-dependent nephrotoxicity. Co-administration of corticosteroids or ACTH can exacerbate hypokalemia. Anemia is sometimes seen, and bone marrow toxicity of ganciclovir is exacerbated by amphotericin B. Finally, probenecid may increase the plasma levels of amphotericin B.

Azoles

The most common side effects for all of the azoles include anorexia, nausea, and vomiting. Other side effects include rash, headache, and potential hepatotoxicity (especially with ketoconazole). The azoles should be used with caution, in patients on medications metabolized via the CP450 system, due to their numerous clinically significant interactions (153). Unique adverse effects from specific azoles include: diminished testosterone and cortisol levels with ketoconazole; mineralocorticoid excess with itraconazole (less so with ketoconazole); cardiac dysrhythmias with itraconazole; and transient, reversible visual changes (seen only with voriconazole).

Echinocandins

Caspofungin is generally well tolerated with minimal side effects. Caspofungin interacts with cyclosporine (increasing the risk of liver toxicity), and tacrolimus (increasing clearance, thereby decreasing available tacrolimus). Minor dosage adjustments are necessary with these drugs and are outlined in the package insert. Micafungin and anidulafungin have none of the above listed drug interactions. Anidulafungin must be reconstituted in alcohol for infusion and, therefore, risks inducing a disulfiram-like reaction if given to a patient also receiving metronidazole; administration of anidulafungin also required a larger volume (up to 500 mL) for infusion, which may present a problem for fluid management in an ICU patient.

Therapeutic/Clinical Uses

The choice of anti-fungal therapy may be complex due to the numerous anti-fungal agents with different mechanisms of action, spectrum of activity, various adverse effects, and the paucity of comparative studies. ♂ **Amphotericin B remains the reference standard by which all anti-fungals are measured. For fungi known to be resistant, other agents including the azoles and echinocandins may be considered in the treatment of systemic infections (154).** ♂ The option of treating with enteral antifungals has also been recently recognized with agents that have excellent oral bioavailability (fluconazole, itraconazole suspension, and voriconazole).

The newer liposomal preparations of amphotericin B are significantly more expensive than amphotericin B deoxycholate but are also less toxic. Caspofungin and micafungin are similar in expense to liposomal amphotericin B. The

Table 15 Antimicrobial Drugs of Choice Against Selected Viruses (Tables 16–18)

Microorganisms	Drug of Choice	Alternative agents
Cytomegalovirus	Ganciclovir	Foscarnet, cidofovir, valganciclovir
Herpes simplex	Acyclovir	Ganciclovir, foscarnet, valacyclovir, famciclovir
Herpes zoster	Acyclovir	Foscarnet, penciclovir, famciclovir, valacyclovir
Influenza	Oseltamavir, rimantidine	Zanamavir, amantadine

enterally effective azoles are much less expensive alternatives via that route. Therefore, the choice of antifungal agent(s) must take into account the specific mold or yeast suspected or proven, local epidemiologic patterns (especially non-albicans *Candida* spp. infection), severity of illness, ability to take oral medication, toxicities, allergies, drug–drug interactions, and cost.

Guidelines for the treatment of *Aspergillus* infections have recently been reviewed (155,156), and practice guidelines for the treatment of *Candida* infections have also been published (157,158).

There are no prospective RCTs available that describe the use of putatively synergistic combinations of antifungals although these treatment strategies appear reasonable based upon the respective mechanisms of action. For instance, the combination of an azole, like voriconazole, with caspofungin make intuitive sense since the azoles inhibit ergosterol synthesis and caspofungin works on the cell wall, which are separate biochemical pathways. In a similar vein, the combination of caspofungin and amphotericin formulations would appear to be a useful combination. The use of multiple anti-fungal agents has been used anecdotally in case reports and case series (159,160). However, azoles should not be used together with amphotericin B because they are antagonistic.

ANTIVIRALS

Antiviral agents will be discussed in terms of viral infections that are commonly seen in the critical care unit (Table 15). Antiretroviral agents, used for patients infected with the human immunodeficiency virus (HIV), will not be discussed, but the interested reader may refer to recently published treatment guidelines (161–163). Antimicrobials useful for the prophylaxis of opportunistic infections in patients with HIV infection were recently reviewed (164).

♂ **Currently there are more than a dozen antiviral drugs commercially available in the US for the treatment and/or prophylaxis of viral infections. Most of these drugs function as nucleoside analogs and can be conveniently divided into drugs useful for herpes virus infections, influenza infection (165), hepatitis viruses (166), and miscellaneous viral infections.** ♂ Several recent reviews of antiviral drugs are noted (167–169).

Herpes Virus Antivirals

The most common viral infections seen in the ICU are due to one or more of the herpes viruses that include herpes simplex virus (HSV) (Table 16), Varicella-zoster virus

Table 16 Antiviral Agents for Herpes Simplex Virus Infections

Viral infection	Drug	Route	Usual dosage
Genital herpes ^a	Acyclovir	PO or IV	400 mg tid for 5–10 days
	Famciclovir	PO	250 mg tid for 7–10 days
	Valacyclovir	PO	1 g bid for 10 days
Herpes encephalitis	Acyclovir	IV	10 mg/kg every 8 hr in 1-h infusion for 14–21 days
Mucocutaneous disease in immunocompromised hosts	Acyclovir	IV	5 mg/kg every 8 hr for 7–14 days
		PO	400 mg five times daily for 7–14 days
	Ganciclovir	IV	5 mg/kg every 8–12 hr for 7 days
	Famciclovir	PO	500 mg bid for 7 days
Orolabial herpes	Penciclovir 1%	Topical	q2 hr while awake for 4 days
Keratoconjunctivitis ^b	Trifluridine 1%	Topical—solution	One drop, every 2 hr up to 9 drops/day
	Vidarabine 3%	Topical—ointment	1/2 inch ribbon five times daily

^aIn acyclovir-resistant in HSV or VZV infections, IV foscarnet 40 mg/kg every 8 hr appears beneficial.

^bTreatment of HSV ocular infections should be supervised by an ophthalmologist.

Abbreviations: HSV, herpes simplex virus; IV, intravenously; PO, per OS; VZV, varicella–zoster virus.

Table 17 Antiviral Agents for Varicella–Zoster Virus Infections^a

Viral infection	Drug	Route	Usual dosage
Varicella in normal adults	Acyclovir	PO	20 mg/kg up to 800 mg qid for 5 days
Varicella in immunocompromised hosts	Acyclovir	IV	500 mg every 8 hr for 7–10 days
Zoster in normal hosts	Acyclovir	PO	800 mg five times daily for 7–10 days
	Valacyclovir	PO	1 g tid for 7 days
	Famciclovir	PO	500 mg tid for 7 days
Zoster in immunocompromised hosts	Acyclovir	IV	10 mg/kg every 8 hr in 1-hr infusion for 7 days

^aIn acyclovir-resistant in HSV or VZV infections, IV foscarnet 40 mg/kg every 8 hr appears beneficial.

Abbreviations: HSV, herpes simplex virus; IV, intravenously; PO, per OS; VZV, varicella–zoster virus.

(VZV) (Table 17), (reviewed in Gnann) (170) and cytomegalovirus (CMV) (Table 18). There are a variety of antivirals available for the treatment and/or prophylaxis of the various herpes virus infections.

Acyclovir, the first orally available anti-herpes drug, is a nucleoside analog and is available in both enteral and parenteral forms. Because of its poor oral bioavailability, a unique pro-drug, a covalent conjugate of valine and acyclovir, has been developed into the pro-drug valacyclovir (the pro-drug). Valacyclovir is converted to acyclovir by a host enzyme in the intestinal mucosa, leading to improved bioavailability of acyclovir. Similarly, famciclovir, which is available only in an oral preparation, is a pro-drug of penciclovir.

Famciclovir has essentially the same spectrum of activity as acyclovir but with improved oral bioavailability.

Ganciclovir differs only slightly from acyclovir structurally and, in addition to the herpes virus spectrum of acyclovir, also is active against CMV. An oral preparation of ganciclovir is available; however, its poor oral bioavailability recently led to the development of valganciclovir, an orally available pro-drug of ganciclovir, which is metabolized in the same manner as valacyclovir.

Foscarnet is an analog of inorganic pyrophosphate and complexes with DNA polymerase, thereby inhibiting viral DNA synthesis. This agent is useful against all of the herpes viruses, including CMV. Its clinical use is not

Table 18 Antiviral Agents for CMV Infections

Viral infection	Drug	Route	Usual starting dosage
CMV retinitis	Ganciclovir	IV	5 mg/kg every 12 hr in 1-hr infusion for 14–21 days
	Ganciclovir	Oral	1000 mg every 8 hr for 21 days
	Valganciclovir	Oral	900 mg every 12 hr for 21 days
	Cidofovir	IV	5 mg/kg weekly for two doses
	Formivirsen	Intravitreal	330 µg every 2 weeks
	Foscarnet	IV	60 mg/kg every 8 hr in 1–2 hr infusion for 14–21 days
CMV pneumonia	Ganciclovir	IV	5 mg/kg every 12 hr in 1-hr infusion + IV immunoglobulin for 14–21 days (in BMT patients)

Abbreviations: BMT, bone marrow transplant; CMV, cytomegalovirus; IV, intravenously.

Table 19 Antiviral Agents for Hepatitis B and C Infections

Viral infection	Drug	Route	Usual dosage
Chronic hepatitis B	Interferon- α	SC	10 MU three times weekly or 5 MU daily
	Lamivudine	PO	100 mg/day
	Adefovir	PO	10 mg/day
	Entecavir	PO	0.5–1 mg/day
Chronic hepatitis C	Peginterferon alfa-2a ± Ribavirin	SC	180 mcg weekly
		PO	800–1200 mg/day depending on weight and genotype
	Pegylated interferon alfa-2b ± Ribavirin	SC	1.0–1.5 mcg/kg weekly
		PO	800–1200 mg/day depending on weight and genotype
	Interferon alfa-2a	SC/IM	3 MU three times weekly
	Interferon alfa-2b	SC/IM	3 MU three times weekly
	Interferon alfacon-1	SC	9 mcg three times weekly

Abbreviations: IM, intramuscular; PO, per OS; SC, subcutaneously.

popular, however, because of its toxicities (nephrotoxicity and electrolyte abnormalities), and it is generally reserved for mainly for acyclovir-resistant HSV and CMV infections.

Cidofovir is a phosphonate nucleotide analog that is available intravenously for the treatment of cytomegalovirus infection. It is only useful intravenously. Its use is complicated by nephrotoxicity and renal tubular acidosis, and it is generally reserved for patients who have failed or have a contraindication to ganciclovir. Dosing guidelines for drugs used to treat HSV and CMV infections are shown in Tables 16 to 18.

Hepatitis B and C Antivirals

Hepatitis B and C are notable causes of chronic hepatitis and cirrhosis. Treatment for acute hepatitis is generally supportive in nature. Many patients in an ICU setting having liver disease and antiviral treatment for hepatitis B and C are discussed in this context. Ribavirin is a guanosine analog that inhibits ribonucleoprotein synthesis, is active against many RNA viruses, including infections caused by hepatitis C virus (especially in combination with interferon), and hemorrhagic fever viruses. Its major toxicity is anemia that can be clinically quite significant. Lamivudine (3TC) is a nucleoside that is useful for both HIV infection and hepatitis B virus infection. Adefovir, which was originally used for HIV but taken off the market due to nephrotoxicity at higher doses, can be used in much lower doses to treat hepatitis B. Tenofovir, a congener of adefovir, can also be used for

both hepatitis B and HIV. Interferon-alpha and polyethylene glycol-conjugated forms of interferon are also used as antivirals for infections caused by hepatitis B and hepatitis C infections. They are generally poorly tolerated, must be given parenterally (subcutaneously), must be taken over a long period of time, and frequently cause a flu-like syndrome. Treatment of hepatitis B and C are reviewed elsewhere (171–174). Refer to Table 19 for antiviral drug useful in the treatment of Hepatitis B and Hepatitis C infections.

Influenza Antivirals

Influenza, (and its sequelae) is the major cause of respiratory failure in and outside of the US. Influenza vaccines, which are manufactured annually, according to which subtypes are judged to be the most likely epidemic strains, can prevent a large majority of the cases of severe illness. There are also several drugs that are available for the prophylaxis and treatment of influenza virus infections. Two of the older drugs, amantadine and rimantadine are oral agents that inhibit the replication of only influenza A virus but not influenza B virus. Two newer agents inhibit the replication of both influenza A and B viruses: oral oseltamivir (Tamiflu[®]) and inhaled zanamivir (Relenza[®]). Please refer to Table 20 for dosing guidelines recommendations.

IMMUNOMODULATORS: ACTIVATED PROTEIN C

History/Description

Despite advances in critical care, the rate of death from severe sepsis still ranges from 30% to 50%. Though all the mechanisms of sepsis have yet to be elucidated, our understanding of this complex condition has greatly increased in the past decade (Volume 2, Chapter 47). This has led to the development of compounds that interrupt the detrimental inflammatory and coagulation process involved in sepsis. One such development is drotrecogin alfa (Xigris[®]), a recombinant version of natural human plasma-derived activated protein C (APC). Several studies have reviewed this agent (175–177). Kox (178) recently reviewed other immunomodulator agents for sepsis and two reviews of the treatment of sepsis were recently published by Wheeler (179) and Healy (180) and will not be discussed further. Refer also to Volume 2, Chapter 47 for a discussion on sepsis and Volume 2, Chapter 63 for a review of SIRS.

Table 20 Antiviral Agents for Treatment of Influenza Virus Infections^a

Viral infection	Drug	Route	Usual dosage
Influenza A or B virus	Oseltamivir	PO	75 mg bid for 5 days
	Zanamivir	Aerosol	10 mg bid by inhaler for 5 days
Influenza A virus	Amantadine	PO	100 mg bid for 5 days for treatment
	Rimantadine	PO	200 mg/day for 5 days for treatment

^aDifferent doses used for prophylaxis.

Abbreviation: PO, per OS.

Mechanism of Action, Pharmacology, Administration, and Dosage

The antithrombotic effects of APC are mediated by inactivation of clotting factors Va and VIIIa. APC also increases fibrinolytic activity by inhibiting plasminogen-activator inhibitor 1 (PAI-1), which increases endogenous tissue-plasminogen activator (t-PA). In vitro data suggests that APC exerts anti-inflammatory effects by inhibiting the production of the inflammatory cytokines TNF- α , interleukin-1 (IL-1), and interleukin-6 (IL-6) by monocytes and by limiting the rolling of monocytes and neutrophils along injured endothelium.

The average half-life after a 24 mcg/kg/hour infusion of APC is 1.2 hours. This is five times longer than the average half-life of native APC. APC is metabolized and inactivated by endogenous plasma protease inhibitors. There is a linear relationship between APC concentrations and activated partial thromboplastin time (aPTT) response in healthy patients. To date, no patients with sepsis have been re-administered APC. Antibodies to the recombinant APC (drotrecogin alfa) have been detected in two patients during phase II and III trials. One of the patients with neutralizing antibodies developed superficial and deep vein thrombi and died of multi-organ failure.

The dosage of APC is 24 mcg/kg/hour infused intravenously for 96 hours. The drug must be infused within 24 hours from the time of reconstitution or preparation. Patients with end-stage renal disease were excluded from phase III studies. However, in six non-septic ESRD patients, APC was not cleared by dialysis, and patients had clearance rate similar to patients without ESRD.

Adverse Effects and Drug Interactions

The most common adverse event associated with APC is bleeding, which is consistent with the drug's antithrombotic activity. Bleeding occurred in 25% of treated patients and 18% of placebo-treated patients in the Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis (PROWESS) trial. However, the frequency of serious bleeding with APC was only 3.5%, compared to 2.0% in the placebo-treated patients, but this difference was not clinically or statistically ($P = 0.06$) significant (177). Serious bleeding tended to occur mostly during the infusion period and in patients with predisposing conditions such as gastrointestinal ulceration, traumatic injury to a blood vessel, highly vascular organ injury, or markedly abnormal coagulation values. Relatively uncommon side effects found in phase I trials included headache, ecchymoses, diarrhea, and pain at the site of injection.

Because the major adverse effect of APC is bleeding, concomitant administrations of medications that also increase the risk of bleeding are relatively contraindicated. These medications include the use of unfractionated heparin at >15,000 units/day within eight hours of drug infusion; LMWH at any dose higher or more frequent than recommended by their package inserts within 12 hours of drug administration; warfarin if used within seven days of APC infusion or warfarin-type medications within <5 half-lives at the time of drug administration and the PT >13.3 seconds, and/or INR > 3.0; antiplatelet drugs (ticlopidine or clopidogrel) or ASA >650 mg/day or compounds that contain ASA >650 mg/day within seven days prior to drug administration; thrombolytic therapy (unless used to treat an intra-catheter thrombosis) within three days of drug administration (e.g., streptokinase, tPA, rPA, and

urokinase); glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) within seven days of drug administration; antithrombin infusion of >10,000 units received within 12 hours of drug administration; and protein C concentrate infusion within 24 hours of drug administration.

Therapeutic/Clinical Uses

♣ The PROWESS study demonstrated a statistically significant decrease in 30-day mortality in septic patients treated with APC. ♣ However, safety and economic concerns have led to the development of strict usage criteria for APC at most institutions. There are absolute and relative contraindications to the use of APC. Absolute contraindications are active bleeding, epidural anesthesia, intracranial hemorrhage, retroperitoneal bleeding, and recent major surgery. Relative contraindications include those patient populations excluded from the PROWESS trial and for which no data exist. These relative contraindications include pregnant or breastfeeding mothers, platelet count <30,000/mm³, and age <18 years. The cost of a complete course of APC therapy is approximately \$7,000 to \$10,000.

EYE TO THE FUTURE

Microbes are developing resistance to a number of previously efficacious antimicrobials. Accordingly, new modalities are being explored and developed to combat microbial pathogens. New vaccines targeted at nosocomial pathogens are being assessed that may lead to infection prevention in this patient population (181,182). Antibiotics specifically designed with activity against emerging resistant organisms are currently under investigation (183). Antibacterial agents in development showing clinical promise include fluoroquinolones (184–186), ketolides (187,188), oxazolidinones (189–193), everninomycins (194), carbapenems (195–198), glycopeptides (199–201), and glycolcyclines (202–203). Likewise, many new and novel antifungal (204–208) and antiviral (209–213) agents are in clinical development.

A potentially helpful addition to preventing staphylococcal infections has emerged recently with the use of a vaccine (StaphVAX[®]) for the prevention of *S. aureus* infections in chronic dialysis patients, a group of patients who are susceptible to repeated line associated infections (214). The vaccine consists of a mixture of type 5 and type 8 capsular polysaccharides conjugated to a carrier protein, and immunization of dialysis patients decreased *S. aureus* infections by 64% at 32 weeks post immunization as compared to controls. Unfortunately, immunity wanes within a year, so annual vaccinations are necessary. Future vaccines might contain more serotypes. Further, it remains an open question as to whether the protection seen in patients with chronic renal failure can be extended to other sets of patients.

Better insight into the understanding of septic shock will bring us additional agents targeted to alter the natural history of this most feared complication of infection (215–219). In addition, many immunomodulatory therapies are being investigated for severe sepsis and septic shock (220,221). To date, more than 70 phase II and phase III RCTs have been performed evaluating the potential role of adjuvant mediator-targeted therapy in patients with sepsis. A great deal has been learned from these investigations and the future of sepsis research holds not only the prospect of fundamental new insights into the interaction of the host, the environment, and medical intervention in disease

pathogenesis, but also the possibility that a major cause of global morbidity and mortality can be successfully confronted (222).

Adjunctive immune therapy using immunomodulatory therapies and combination antifungal therapy are being explored to help combat the ever-increasing spectra of encountered fungal infections (223–229). Resolution of invasive fungal infections is dependant on host defenses. Clinical trials utilizing granulocyte colony-stimulating factor and interferon products are currently underway that will hopefully establish whether immunotherapy is of clinical value in the treatment of invasive fungal infections (229).

Newly discovered antimicrobial peptides (AMPs) are being studied to help overcome bacterial resistance that

currently hampers our ability to treat many hospital-acquired infections (230–232). AMPs have a broad antimicrobial spectrum and lyse microbial cells by interaction with biomembranes. They also have multiple roles as mediators of inflammation that can influence diverse processes such as cell proliferation, immune induction, wound healing, cytokine release, chemotaxis, and protease-antiprotease relationship. Studies are currently ongoing investigating the biology of AMPs that will hopefully determine their place in therapeutics for infectious and inflammatory diseases (231).

In addition, exciting research is currently underway investigating the newly discovered Type III secretion systems common to several important bacteria and may prove to be a beneficial new target for combating these

Table 21 Antibiotic Guidelines for Trauma Patients

Site/diagnosis	Potential organisms	Primary therapy	Alternative therapy
Aspiration pneumonia during traumatic event	Oral flora	Clindamycin or third-generation cephalosporin ^a	Fluoroquinolone + clindamycin or metronidazole
Closed head injury with ventriculostomy	<i>Staphylococcus aureus</i> , coagulase-negative staphylococci	Need for prophylaxis controversial	Oxacillin ^b or cefazolin or vancomycin
Open head injury	<i>S. aureus</i> , GNR	Ceftriaxone + oxacillin ^b	Vancomycin
Post-brain injury abscess	<i>S. aureus</i> , GNR (including <i>Pseudomonas</i>), anaerobes	Ceftazidime + metronidazole + oxacillin ^b	Meropenem + vancomycin
Blunt chest trauma	n/a	Antibiotics not recommended	n/a
Chest tube prophylaxis	n/a	Antibiotics not recommended	n/a
Blunt abdominal trauma			
Without visceral penetration	n/a	Antibiotics not recommended	n/a
With visceral penetration	Enteric GNR, enterococcus	Ampicillin + third-generation cephalosporin ^a + metronidazole	Vancomycin + fluorquinolone or aminoglycoside ^c + metronidazole or carbapenem or piperacillin/tazobactam
If gastric rupture involvement	<i>Candida albicans</i>	Fluconazole	Voriconazole or caspofungin or amphotericin B
Gunshot wound abdomen	GNR, anaerobes, enterococcus	Ampicillin + third-generation cephalosporin or fluoroquinolone + metronidazole	Vancomycin or piperacillin/tazobactam or carbapenem ± aminoglycoside ^c + metronidazole
Biliary trauma	GNR, enterococci, anaerobes (less often)	Ampicillin or piperacillin + an aminoglycoside ^c	Add metronidazole if initial therapy is unsuccessful
Renal trauma			
Nicked ureter	n/a	Antibiotics not recommended	n/a
Nicked kidney	Follow urine cultures and treat accordingly	n/a	n/a
Orthopedic			
Grade I	<i>S. aureus</i>	Cephalosporin ^{b,d}	Oxacillin or vancomycin
Grade II	<i>S. aureus</i>	Cephalosporin ^{b,d} + aminoglycoside ^c	Oxacillin or vancomycin + an aminoglycoside ^c
Grade III	<i>S. aureus</i> ; GNR; possible anaerobes	Cephalosporin ^{b,d} + an aminoglycoside ^c ± metronidazole or clindamycin	Vancomycin + an aminoglycoside ^c ± metronidazole or clindamycin
Acute burns			
Topical	<i>S. aureus</i>	Topical sulfadiazine or sulfamylon	Nitrofurazone
Inhalational	n/a	Antibiotics not recommended	n/a

^aCefotaxime, ceftriaxone, ceftazidime.

^bVancomycin if methicillin-resistant *S. aureus* is common.

^cGentamicin, tobramycin, amikacin.

^dFirst-generation cephalosporin (cefazolin, cephalothin).

Abbreviation: GNR, gram-negative rods.

pathogenic bacteria. In the 1980s and 1990s researchers studying *Yersinia* (the causative agent of bubonic plague) discovered that these organisms utilized a syringe-like injection system to deliver virulence factors inside the mammalian host cell (233). These have since been called Type III secretion systems, and significant homology exists across several species of pathogenic gram-negative organisms (including *Yersinia*, *E. coli*, *P. aeruginosa*, *B. pertussis*, *Salmonella*, *Shigella*, as well as *Chlamydia* spp, and various plant and fish pathogens) (234). Further study of these flagella-like structures likely be a source of anti-infective therapy in the not so distant future (235).

Finally, the field of pharmacogenomics is a rapidly emerging discipline of interest in medicine and pharmaceutical research and development. Pharmacogenomics may have considerable and significant impact on infectious disease therapy, including antibiotic therapy. The last few

years have witnessed an enormous increase in genomic-related technologies as they apply to antibacterial therapies (237). Pharmacogenomics has the potential to revolutionize the prevention, diagnosis, and treatment of infectious diseases (238–245).

SUMMARY

Many patients with severe illness or conditions like multiple trauma and severe burns are susceptible to infection due to their depressed immune function. The goal of antimicrobial therapy is to prevent an infection from developing or to treat an existing infection. In this chapter we have reviewed a multitude of antimicrobials, including antibacterials, antifungals, and antivirals, that are currently available to the clinician for utilization in preventing or treating infections

Table 22 Empiric Antibiotic Therapy for the Critically Ill Intensive Care Unit Patient

Anatomic site/ diagnosis	Potential organism	Primary therapy	Alternative therapy
Blood/bacteremia — line associated— endocarditis	<i>Staphylococcus aureus</i> coagulase-negative- staphylococci GNR	Oxacillin ^a or nafcillin ^a + an aminoglycoside ^b (if enterococcus is suspected. add ampicillin)	Vancomycin or cephalosporin ^d + an aminoglycoside ^b
		A third-generation cephalo- sporin ^c + aminoglycoside ^b	Imipenem or meropenem or piperacillin/tazobactam or azteonam or fluorquinolone + aminoglycoside ^b
CNS/meningitis	<i>Streptococcus</i> <i>pneumoniae</i> <i>Neisseria meningitidis</i> GNR. <i>S. aureus</i>	Ceftriaxone + vancomycin ^c	Imipenem or meropenem
		Penicillin Oxacillin ^a or nafcillin ^a + ceftriaxone + an aminoglycoside ^b or use ceftazidime in place of ceftriaxone if <i>Pseudomonas</i> suspected	Ceftriaxone or imipenem Vancomycin + ceftriaxone + an aminoglycoside ^b
Intracranial/acute abscess	<i>S. aureus</i>	Oxacillin ^a or nafcillin ^a + an aminoglycoside ^b	Vancomycin
	Anaerobes (commonly subacute)	Add metronidazole	Chloramphenicol
Lungs/pneumonia	<i>S. aureus</i>	Oxacillin ^a or nafcillin ^a	Cephalosporin ^d or vancomycin or linezolid
	GNR, oral anaerobes	Third-generation cephalosporin ^c + metronidazole	Fluoroquinolone or imipenem or piperacillin (+clindamycin) or piperacillin/tazobactam + an aminoglycoside ^b
Abdomen/peritonitis. abscess	GNR, anaerobes, enterococci	Ampicillin or piperacillin + metronidazole + an aminoglycoside ^b (if <i>Pseudomonas</i>)	Vancomycin in place of penicillin + metronidazole + an aminoglycoside ^b or third-generation cephalosporin ^c ; imipenem or piperacillin/tazobactam
Abdomen/biliary tract	GNR, enterococci, anaerobes (occur late and in the elderly)	Ampicillin or piperacillin + an aminoglycoside ^b	Add metronidazole if initial therapy is unsuccessful
Pelvis/PID	GNR/anaerobes	Gentamicin and clindamycin	Cefoxitin and doxycycline
Urinary tract/ pyelonephritis	GNR, enterococci	Ampicillin or vancomycin + an aminoglycoside ^b	Third-generation cephalosporin (with ampicillin or vancomycin if entero- coccus suspected)

^aVancomycin if methicillin-resistant *S. aureus* common.

^bGentamicin, tobramycin, amikacin.

^cCefotaxime, ceftriaxone, ceftazidime.

^dFirst-generation cephalosporin (cefazolin, cephalothin).

^eIn areas with high incidence of penicillin-resistant *S. pneumoniae*, vancomycin should be added.

Abbreviations: GNR, gram-negative rods; PID, pelvic inflammatory disease.

in critically ill patients. In addition, we have highlighted many areas currently being investigated with the quest of identifying additional agents to assist in the control of antibiotic-resistant bacteria and opportunistic infections.

Antibiotic use should be planned deliberately from the time of admission in hospitalized patients. Prophylactic antibiotic use should be restricted to a specific diagnosis and exceptional conditions. The antibiotic choice should be determined based on prevailing, institution-specific bacterial resistance patterns. Only through judicious antimicrobial use can prevention of the development of multi-resistant pathogens be realized. The choice of antimicrobial agent must be influenced by a clinician's familiarity with the available drugs. Empiric guidelines for Trauma patients are provided in Table 21, and those for critically ill patients of trauma, surgical, or medical origin are shown in Table 22.

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The authors wish to dedicate this chapter to their colleague, Lee Rickman, who tragically died during the preparation of this manuscript. We also wish to recognize his immense contributions to patient care in San Diego, infectious disease education around the world, and to his insightful and enthusiastic assistance with this chapter prior to his passing.

KEY POINTS

- Antimicrobial selection for trauma and critical care is based on the following seven considerations: (i) whether the antibiotics are planned for prophylaxis or treatment of an established infection; (ii) the anatomic site of infection; (iii) whether the infection is community-acquired or nosocomial; (iv) best guess of the most probable causative microorganism (based upon geographical and institutional isolate profiles); (v) the patient's innate immunological status; (vi) the severity of the infection and general condition of the patient; and (vii) financial cost.
- A primary tenet of antimicrobial therapy is to use the narrowest spectrum antibiotic possible, rather than a broad-spectrum agent.
- As Ignaz Phillip Semmelweis discovered 150 years ago, the most important means of preventing the transmission of micro-organisms from one patient (via the doctor or nurse) to another patient is strict hand washing (and now, the use of clean disposable gloves).
- At present, the majority of infections in hospitalized trauma patients are due to gram-positive organisms (19) for example, MRSA and VRE and to a lesser extent, multi-resistant gram-negative rods (20).
- Penetrating intra-abdominal injury, perforated abdominal viscera, and open fractures, all warrant antibiotic prophylaxis (22–25).
- The addition of a beta-lactamase inhibitor to beta-lactam antibiotics produces efficacy against beta-lactamase producing organisms, such as *S. aureus*, *E. coli* and most anaerobic bacteria. However, these combo products add no additional activity against *Pseudomonas aeruginosa* and have no activity against MRSA.
- In general, as one selects a second, third or fourth generation cephalosporin, there is increased activity

- against aerobic gram-negative bacteria and less activity against gram-positive organisms.
- The cephamycins, specifically cefoxitin and cefotetan, have unique broad-spectrum activity against most anaerobic organisms (except there are increasing resistant forms of *B. fragilis*).
- Aztreonam is devoid of antibacterial activity against gram-positive and anaerobic bacteria.
- Carbapenems are the class of antibiotics with the greatest spectrum activity of any class of antibiotics for systemic use in humans. They are active against gram-positive (except MRSA), gram-negative, and anaerobic bacteria. These agents (except ertapenem) are particularly useful for hospital-acquired infections where bacterial resistance (other than MRSA and VRE) may be a concern.
- Patients with a history of penicillin allergy due to rash or pruritus only occurring more than three days after administration are no more likely to have any allergic reaction to a cephalosporin than patients without a history of penicillin allergy, and can safely receive cephalosporins.
- There is up to a 50% chance of developing a rash to carbapenems in patients with a history of rash to penicillins.
- Aztreonam is considered a safe alternative in patients allergic to penicillins or cephalosporins requiring gram-negative coverage, and vancomycin is the recommended choice for those patients requiring gram-positive coverage.
- All aminoglycosides are nephrotoxic and ototoxic and can prolong the duration of neuromuscular blockade drugs.
- Tetracycline has a broad spectrum of antimicrobial activity including gram-positive, gram-negative, and anaerobic bacteria, as well as rickettsias, mycoplasma, chlamydias, protozoa, actinomycetes, and certain viruses.
- Azithromycin has an extremely long intracellular dwell time, permitting once daily (or less often) dosing.
- Because of its gram-positive and anaerobic coverage, clindamycin is useful (with combination gram-negative therapy) for necrotizing fasciitis, most oral and vaginal anaerobic infections, and diabetic foot infections, which tend to be polymicrobial and virulent.
- Metronidazole is indicated for the treatment of serious polymicrobial infections involving anaerobes (e.g., necrotizing fasciitis and infections involving contamination from the GI tract). Importantly, other agents with aerobic gram-positive and gram-negative coverage must be coadministered.
- Bacteroides fragilis* is probably the most frequently encountered clinically significant anaerobe and metronidazole should be considered the drug of choice, especially in intra-abdominal infections (57).
- The greatest utility of quinupristin/dalfopristin, daptomycin, and linezolid is in the management of patients with VRE or MRSA infections for which limited alternatives exist.
- Vancomycin is most often used parenterally to treat MRSA, empirically in life-threatening infections, and orally for *C. difficile* colitis.
- TMP/SMX may be extremely useful in severe infections caused by susceptible organisms in the critically ill patient, especially those infections caused by *Enterobacter* sp., and other gram-negative rods that may be multi-resistant to beta-lactam drugs.
- Quinolone antibiotics, similar to the cephalosporins, are traditionally categorized into first to fourth generations based upon spectrum of activity. In general, the second, third, and fourth generations have enhanced

gram-positive cocci activity (except ciprofloxacin) and gram-negative rod activity. Excellent anaerobic activity is seen with trovafloxacin and moxifloxacin.

SSD represents a compromise between the high efficacy of mafenide and the high maintenance of silver nitrate. It is therefore the most commonly employed topical antimicrobial agent in the burn patient, and frequently used as combination treatment (often alternating every 12 hours) with mafenide.

Although many anti-TB agents are available, the most important drugs for therapy of critically ill patients are commonly known as "RIPE" which stands for: rifampin, isoniazid, pyrazinamide, and ethambutol (49,50).

Amphotericin B remains the reference standard by which all anti-fungals are measured. For fungi known to be resistant, other agents including the azoles and echinocandins may be considered in the treatment of systemic infections (151).

Currently there are more than a dozen antiviral drugs commercially available in the United States for the treatment and/or prophylaxis of viral infections. Most of these drugs function as nucleoside analogs and can be conveniently divided into drugs useful for herpesvirus infections, influenza infection (162) hepatitis viruses (163), and miscellaneous viral infections.

The PROWESS study demonstrated a statistically significant decrease in 30-day mortality in septic patients treated with APC.

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