

NOSOCOMIAL GRAM-NEGATIVE INFECTIONS



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Learning Objectives

1. Evaluate the risk factors for gram-negative nosocomial infection and antimicrobial resistance for patients in the intensive care unit.
2. Apply your understanding of the mechanisms of resistance common to gram-negative bacteria in nosocomial disease, including extended-spectrum β -lactamase production, porin channel deletion or structural changes, and efflux pump expression, to empiric antibiotic drug selection for nosocomial pneumonia, urinary tract infection, and bacteremia.
3. Formulate a systems approach to improving the administration of appropriate empiric antibiotic therapy.
4. Given pertinent clinical and laboratory data, design an appropriate treatment plan for a patient with nosocomial gram-negative infection.
5. Evaluate the newer therapies available for managing gram-negative bacteria against traditional antibiotic drugs for empiric treatment of nosocomial infection.

Introduction

Gram-negative bacteria are typically non-pathogenic in the immunocompetent host. This is especially true of the Enterobacteriaceae and the nonfermentative gram-negative bacilli. However, in the debilitated host, gram-negative bacteria can become significant pathogens. Our ability to prevent and treat gram-negative nosocomial infection is largely hampered by antimicrobial resistance, a phenomenon well described in these bacteria. Selecting appropriate empiric antimicrobial therapy has become one of the most important aspects of care when treating nosocomial infection for pharmacists and other clinicians. Many studies have documented excess mortality in patients

who receive initial therapy that does not have activity against the causative gram-negative pathogen (Table 1-1). Many recent studies have found that the microorganisms associated with inappropriate antibiotic drug therapy are a common group of pathogens. The antimicrobial resistance patterns of these organisms vary from institution to institution. Pharmacists must understand the issues surrounding antibiotic resistance, the epidemiology of resistance and microorganisms in the hospital environment, and effective strategies to help successfully manage nosocomial gram-negative infection.

Changing Epidemiology of Gram-negative Infection

Epidemiology

The frequency of gram-negative bacterial infection in nosocomial disease has varied widely over the past century. Before the introduction of antibiotic drugs in the 1920s and 1930s, gram-negative infection was uncommon. Between 1960 and 1985, the percentage of nosocomial infections caused by gram-negative pathogens increased dramatically. This may have occurred through a process of evolutionary selection, in that antibiotic drugs of that era were active predominantly against gram-positive organisms such as staphylococci and streptococci. Prior exposure to antibiotic drugs was, and remains today, a principal risk for developing gram-negative infection. In later years, gram-positive pathogens became more prominent, most likely because of the introduction of ceftazidime and ceftriaxone in 1985. Since the late 1990s, gram-negative bacteria have once again become prominent pathogens.

Gram-negative pathogens are common in both nosocomial pneumonia and bloodstream infections, two of the most difficult nosocomial infections to manage (Table 1-2). Enterobacteriaceae are the most common cause

Abbreviations in this Chapter

ESBL	Extended-spectrum β -lactamase
ICU	Intensive care unit
MIC	Minimum inhibitory concentration
VAP	Ventilator-associated pneumonia

of gram-negative nosocomial infection; however, nonfermentors, such as *Pseudomonas aeruginosa* and *Acinetobacter* species, are predominant pathogens in the critically ill.

Mortality

The frequency of mortality in gram-negative nosocomial infection remains high. Mortality rates for gram-negative bacteremia have not changed dramatically since the era before antibiotic drugs. Patients with nosocomial ventilator-associated pneumonia (VAP) have higher mortality rates than similar patients without VAP, but the impact is greatest for certain high-risk pathogens, such as *Acinetobacter* species, *P. aeruginosa*, and *Stenotrophomonas maltophilia*. There are several independent risk factors for mortality, including the presence of hepatic, renal, or cardiac failure; diabetes mellitus; age older than 60 years; corticosteroid use; antineoplastic therapy; neutropenia; and shock.

Risk Factors

In the intensive care unit (ICU) setting, severely ill patients at risk for infection are housed in close proximity to other patients who may already be infected or colonized with gram-negative pathogens. Nursing and other personnel shortages have affected the staffing ratios in such a manner that one health care worker may be responsible for several severely ill patients at one time, rather than focusing efforts on just one patient. This increases the risk of cross-contamination among patients through health care worker vectors. Invasive monitoring devices, indwelling urinary and intravascular catheters, endotracheal intubation, and mechanical ventilation are all common risks for nosocomial infection in patients in the ICU. The increasing extension of complex medical care outside the ICU and the hospital means more patients who require hospitalization previously have been exposed to antibiotic drugs, invasive devices and procedures, and are at risk for infection and antibiotic resistance. This shift in patient care has caused an increase in the severity of illness among patients who are cared for in the hospital. The National Nosocomial Infection Surveillance system of the Centers for Disease Control and Prevention reports a 17% increase in the number of ICU beds in the United States from 1988 to 1995, whereas total hospital bed capacity has decreased slightly.

Appropriate Versus Inappropriate Therapy

Despite a vast assortment of antibiotic drugs that have broad-spectrum activity and the increasing use of antimicrobial drugs in the hospital setting nationwide, inappropriate antimicrobial therapy remains a significant problem in treating nosocomial infection. Inappropriate antibiotic therapy can be defined in several terms, including antimicrobial use when it is not indicated, use of an antibiotic regimen that does not have activity against the causative pathogen, incorrect dosing, and wrong administration route. The consequences of inappropriate use can be significant, including increased rates of morbidity and mortality, and increased resistance.

Several investigators have described the outcomes of critically ill patients with nosocomial infection who did not receive empiric antibiotic therapy that was active against the bacteria causing the infection. This inappropriate therapy, even if corrected after culture and susceptibility data were available, led to increased mortality. Numerous studies demonstrated increased mortality associated with inappropriate antimicrobial use in nosocomial infection, including VAP, urinary tract, wound, intra-abdominal, and bloodstream infections. Antimicrobial resistance appears to play an important role in inappropriate antimicrobial prescribing. One report determined that 20% of all ICU cases (nosocomial and community-acquired infection) of inappropriate antimicrobial therapy were caused by resistant gram-negative bacilli. Gram-negative bacteria were responsible for more than 50% of all inadequately treated nosocomial infections. The mortality rate in the patients who received appropriate therapy was 12.2% compared to 52.1% in patients receiving inadequate treatment. Patients who received inadequate therapy were more likely to develop bloodstream infections, sepsis, severe sepsis, and septic shock, and they were more likely to receive vasopressors and mechanical ventilation. Similar studies demonstrated an association between inappropriate therapy and hospital length of stay, ICU length of stay, and duration of mechanical ventilation.

Inappropriate antibiotic therapy largely occurs secondary to resistant bacteria. Increasingly, common gram-negative organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa* have become resistant to several first- and second-line antibiotic drugs. In a recent study of 135 consecutive episodes of VAP, no combination of three antibiotic drugs could be found to empirically cover greater than 88% of the episodes. This makes selecting appropriate empiric antimicrobial therapy immensely difficult. Choosing an appropriate therapy requires an understanding of the resistance mechanisms and their distribution in the nosocomial pathogen milieu. Pharmacists play an important role in antimicrobial drug selection, and may function in the pivotal role of liaison between the microbiology laboratory, the pharmacy and therapeutics committee, and the patient.

Niederman MS. Impact of antibiotic resistance on clinical outcomes and the cost of care. *Crit Care Med* 2001;29(suppl):N114–N20.

Fridkin SK, Gaynes RP. Antimicrobial resistance in the intensive care unit. *Clin Chest Med* 1999;20:303–16.

Garner JS. Guideline for isolation precautions in hospitals. Part I. Evolution of isolation practices, Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1996;24:24–31.

Table 1-1. Mortality in Nosocomial Gram-negative Infections with Appropriate and Inappropriate Antimicrobial Therapy

Reference	Infection	Mortality Rate (%)	
		With Appropriate Therapy	With Inappropriate Therapy (%)
Leibovici L, et al. Scand J Infect Dis 1997;29:71–5.	Sepsis	74.9	84.7
Kollef MH, et al. Chest 1999;115:462–74.	Multiple types	12.2	52.1
Ibrahim EH, et al. Chest 2000;118:146–55.	Bacteremia	28.4	61.9
Valles J, et al. Chest 2003;123:1615–25.	Bacteremia	27	70.4
Iregui M, et al. Chest 2002;122:262–8.	VAP	28.4	69.7

VAP = ventilator-associated pneumonia.

Resistance Issues

Rates

The antimicrobial resistance rate among nosocomial pathogens has increased at an alarming pace over the past 10 years. With more than 2 million nosocomial infections occurring in the United States annually, 50–60% are caused by antimicrobial-resistant strains. Nosocomial infection is thought to contribute to or cause more than 77,000 deaths/year at a cost of \$5–10 billion. The lengths of hospital and ICU stay are increased, and the intensity of therapy, which includes drug therapy, culture and susceptibility testing, and isolation procedures, is greater for patients with resistant organisms, making the attributable cost of infection with these organisms enormously high. Antibiotic-resistant gram-negative bacilli are more commonly identified in the ICU, and are associated with a significantly longer duration of hospital stay, and higher mortality rates than antibiotic-susceptible gram-negative infections. Antibiotic-resistant gram-negative bacilli infection is more commonly associated with resistance to empiric antibiotic therapy, requiring treatment change. The most important gram-negative resistance issues affecting nosocomial infections are extended-spectrum β -lactamases (ESBLs) in *K. pneumoniae*, *E. coli*, *Enterobacter* species, and *Proteus mirabilis*; cephalosporin and extended-spectrum penicillin resistance mediated by AmpC β -lactamase found in *Enterobacter* species and *Citrobacter freundii*; and multidrug-resistant *P. aeruginosa*, *Acinetobacter* species, and *S. maltophilia*.

Factors That Promote Antimicrobial Resistance

Health Care Setting Factors

Many factors may be responsible for the increasing incidence of gram-negative infection. Transmission of antibiotic-resistant pathogens in the acute care setting is common. A variety of health care workers participate in managing acutely ill patients, and handwashing or other

Table 1-2. Top 10 Bacterial Pathogens Associated with Nosocomial Infection: Isolates from Bloodstream Infections and Pneumonia^a

Rank	Bloodstream	Pneumonia
1	<i>Pseudomonas aeruginosa</i>	<i>P. aeruginosa</i>
2	<i>Streptococcus aureus</i>	<i>S. aureus</i>
3	<i>Escherichia coli</i>	<i>E. coli</i>
4	CoNS	<i>S. pneumoniae</i>
5	<i>Enterococcus</i> species	<i>Klebsiella</i> species
6	<i>Klebsiella</i> species	<i>Haemophilus influenzae</i>
7	<i>Streptococcus pneumoniae</i>	<i>Enterobacter</i> species
8	β -Hemolytic streptococci	<i>Serratia</i> species
9	<i>Enterobacter</i> species	<i>Stenotrophomonas maltophilia</i>
10	Viridans streptococci	<i>Acinetobacter</i> species

CoNS = coagulase-negative staphylococci.

^aDiekema DJ, Pfaller MA, Jones RN, et al. Trends in antimicrobial susceptibility of bacterial pathogens isolated from patients with bloodstream infections in the USA, Canada and Latin America. SENTRY Participants Group. Int J Antimicrob Agents 2000;13:257–71 and Hoban DJ, Biedenbach DJ, Mutnick AH, Jones RN. Pathogen of occurrence and susceptibility patterns associated with pneumonia in hospitalized patients in North America: results of the SENTRY Antimicrobial Surveillance Study (2000). Diagn Microbiol Infect Dis 2003;45:279–85.

aseptic techniques are not uniformly or effectively practiced throughout the health care setting. Data suggest that antimicrobial-resistant pathogens are carried from patient to patient on the unwashed hands of health care workers. Increasingly, patients are transferred to the hospital from nursing homes or other institutional facilities for the elderly that serve as breeding grounds for antimicrobial resistance. These patients may be colonized or infected with resistant microbes that are then spread throughout a hospital ward or ICU. Pharmacists are faced with unique challenges in selecting antimicrobial drug therapy in an increasingly drug-resistant world of microorganisms. Pharmacists must function in concert with infection control personnel, other bedside clinicians, and patient family members to educate about proper cleanliness in the hospital, and promote

Sahloff EG, Martin SJ. Extended-spectrum β -lactamase resistance in the ICU. J Pharm Pract 2002;15:96–105.

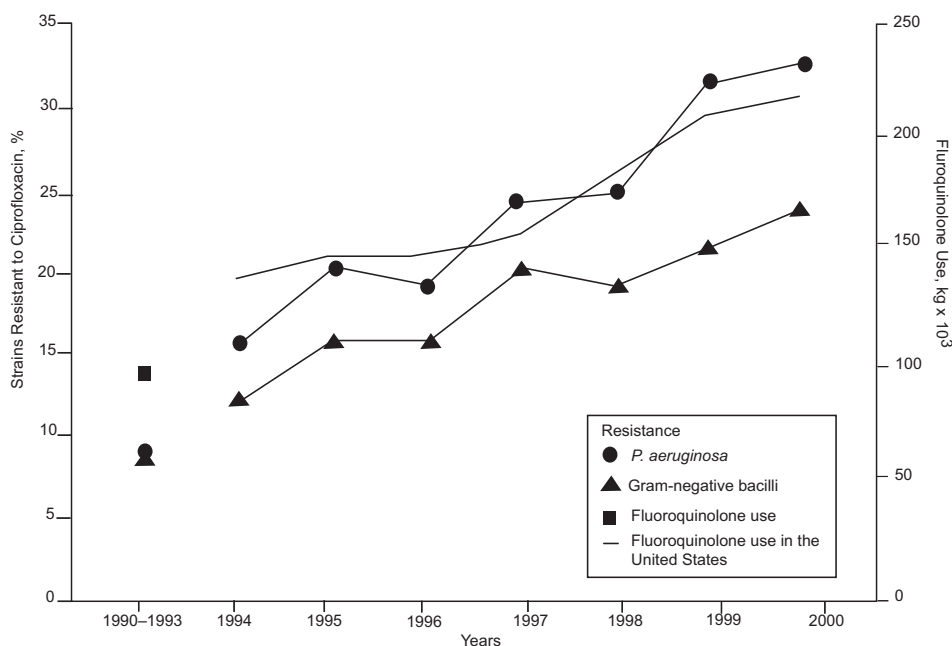


Figure 1-1. Fluoroquinolone use and resistance rates in *Pseudomonas aeruginosa* and Gram-negative bacilli in the United States. Reprinted with permission from the American Medical Association. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 2003;289:885-8.

practices that reduce the likelihood of patient-to-patient transmission of disease.

Patient-specific Factors

Many patient-specific factors increase the infection risk with antimicrobial-resistant pathogens. Acutely ill patients, especially those in the ICU, require invasive monitoring and therapeutic devices. Intensive care unit patients commonly have severe underlying clinical conditions, such as immunosuppression, cancer, malnutrition, organ failure, and prior interaction with the health care system, that place them at an increased risk for colonization or infection with resistant pathogens. Patients with severe disease have longer hospital and ICU stays. Late-onset nosocomial infections among patients in the ICU are more likely to be associated with an antimicrobial-resistant pathogen.

Using antibiotic drugs in hospitalized patients is the most important factor in developing antimicrobial resistance. A correlation between antimicrobial use and antimicrobial resistance has been documented. A recent study demonstrated a significant correlation between increasing rates of ciprofloxacin resistance in *P. aeruginosa* ($r=0.976$) and other gram-negative bacilli ($r=0.891$) with fluoroquinolone use between 1990 and 2000 (Figure 1-1). Extended-spectrum β -lactamase-mediated resistance has been associated with third-generation cephalosporin use. Imipenem use in an institution with significant ESBL-producing *K. pneumoniae* led to a significant

increase in the frequency of imipenem-resistant *P. aeruginosa*. A high percentage of antimicrobial drug use is misdirected at best, and inappropriate at worst. Pharmacists must promote and practice good antimicrobial stewardship throughout the institution to preserve the use of antimicrobial drugs that are available today.

Specific Resistance Mechanisms

AmpC-type β -Lactamase

Most Enterobacteriaceae carry AmpC cephalosporinases, but these enzymes are considered clinically problematic in the so-called SPICE organisms (*Serratia*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*, as well as *Providencia*, *Morganella*, and *Hafnia*). AmpC-mediated β -lactamase confers resistance to first-, second-, and third-generation cephalosporins, in addition to monobactams, such as aztreonam, and to some penicillins. Production of the AmpC enzyme occurs either constitutively (all the time) or after induction (only in the presence of the antibiotic). Expression of the β -lactamase is generated by antimicrobial inducers that have particular affinity for specific penicillin-binding proteins. The most potent inducers are the cephamycins (e.g., cefoxitin) and imipenem. Low-induction potential occurs with cefepime and aztreonam. However, resistance induction also can be generated by first-, second-, and third-generation cephalosporins. Although the AmpC-encoding gene can be present on plasmids, it usually resides on the bacterial chromosome.

Sader HS, Biedenbach DJ, Jones RN. Global patterns of susceptibility for 21 commonly utilized antimicrobial agents tested against 48,440 Enterobacteriaceae in the SENTRY Antimicrobial Surveillance Program (1997-2001). Diagn Microbiol Infect Dis 2003;47:361-4.

Aeschlimann JR. The role of multidrug efflux pumps in the antibiotic resistance of *Pseudomonas aeruginosa* and other gram-negative bacteria. Pharmacotherapy 2003;23:916-24.

Moreover, the AmpC-encoding gene often is present with other antibiotic resistance genes. The *Enterobacter* species may be unique in that there can be high-level AmpC expression and loss of outer membrane porin proteins, resulting in multidrug resistance. AmpC-type β -lactamases hydrolyze broad- and extended-spectrum cephalosporins, including cephamycins, but they are not inhibited by clavulanic acid or other β -lactamase inhibitors. Extended-spectrum β -lactamase-producing organisms and AmpC β -lactamase-producing organisms remain susceptible to carbapenems. Using certain broad-spectrum antibiotic drugs, such as the third-generation cephalosporins, can lead to selection of mutant, resistant bacterial subpopulations producing the AmpC-type β -lactamase. These stably derepressed mutants are not easily detected by a microbiology laboratory at the standard inocula used in susceptibility testing. Being aware of the possibility of stably derepressed AmpC mutants is important for clinical selection of therapeutic β -lactam antibiotic drugs.

Plasmid-mediated AmpC β -lactamases were reported in 1988. Plasmid-mediated AmpC β -lactamases were created through the transfer of chromosomal genes for the inducible AmpC β -lactamase onto plasmids. This transfer resulted in plasmid-mediated AmpC β -lactamases in isolates of *E. coli*, *K. pneumoniae*, *Salmonella* species, *C. freundii*, *Enterobacter aerogenes*, and *P. mirabilis*. To date, all plasmid-mediated AmpC β -lactamases have similar substrate profiles to the parental enzymes from which they appear to be derived. Unlike chromosomal AmpC, plasmid-mediated AmpC is not inducible.

Extended-spectrum β -Lactamase

Extended-spectrum β -lactamases are β -lactamases capable of hydrolyzing penicillins, broad- and extended-spectrum cephalosporins that contain the oxyimino side chain, and monobactams, and are inhibited by clavulanic acid. Extended-spectrum β -lactamases have been isolated from a variety of Enterobacteriaceae, as well as *P. aeruginosa*. Originally, they were found in *K. pneumoniae* and *E. coli*, but are now common in other gram-negative organisms such as the *Enterobacter* species. Genes that code for ESBL are carried on plasmids and can be transferred easily from one organism to another. Extended-spectrum β -lactamase-producing organisms remain susceptible to cephamycins (cefoxitin and cefotetan).

Plasmids that contain genes that code for ESBLs also commonly contain genes that encode for mechanisms of resistance to many other antibiotic drugs, including aminoglycosides, chloramphenicol, sulfonamides, trimethoprim, and tetracycline. The frequency of fluoroquinolone resistance is higher in ESBL-producing organisms than among non-ESBL-producing *K. pneumoniae* or *E. coli*. Both ESBLs and plasmid-mediated AmpC β -lactamases typically are associated with broad multidrug resistance (usually a consequence of genes for other antibiotic resistance mechanisms residing on the same plasmids as the ESBL and AmpC genes). A serious challenge facing clinical microbiology laboratories is that

clinically relevant ESBL-mediated resistance is not always detectable in routine susceptibility tests.

Laboratory determination of ESBL production is hampered by the differing rates of drug influx into the gram-negative periplasmic space. Ceftazidime enters the periplasmic space slowly, making it susceptible to hydrolysis by β -lactamases. Most ESBL-producing organisms appear resistant to ceftazidime in routine in vitro testing. Cefotaxime and ceftriaxone rapidly enter the periplasmic space and are less susceptible to hydrolysis by ESBLs. Routine laboratory testing may report ESBL-producing organisms as susceptible to cefotaxime and ceftriaxone, despite the enzyme activity. The Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) has proposed specific testing on possible ESBL-producing *E. coli* and *Klebsiella* species. Extended-spectrum β -lactamase production is suspected if bacterial growth is observed despite a concentration of 1 mcg/ml of at least one of three extended-spectrum cephalosporins (ceftazidime, ceftriaxone, or cefotaxime) or aztreonam, or growth occurs despite a concentration of 4 mcg/ml of cefpodoxime. Using more than one antibiotic drug for screening improves the sensitivity of detecting ESBLs. Extended-spectrum β -lactamase-production can be confirmed by demonstrating a greater than or equal to 3 serial dilution concentration decrease in minimum inhibitory concentration (MIC) when testing ceftazidime and cefotaxime with the addition of clavulanic acid. Unfortunately, this methodology detects ESBL-producing organisms but not AmpC β -lactamases.

The first report of ESBL-producing organisms in the United States appeared in 1988. It is difficult to determine the exact prevalence of ESBL production among Enterobacteriaceae in the United States because these bacteria can be falsely classified as susceptible according to standard laboratory procedures. The estimated prevalence of ESBL-producing bacteria ranges from 0% to 25%, with a national average of about 3%. The Centers for Disease Control and Prevention reported that in patients in ICUs located in the United States, the rate of extended-spectrum cephalosporin resistance in strains of *E. coli* rose 48% when comparing the 1999 rate to the mean rate of resistance over the preceding 5 years (1994–1998). The rate of extended-spectrum cephalosporin resistance in isolates of *K. pneumoniae* from patients in ICUs located in the United States was 10.4% in 1999. The most recent data on nosocomially acquired infection from the National Nosocomial Infection Surveillance system (through August 2002) reported the incidence of ESBL-producing *E. coli* in the United States at 6.3%, *K. pneumoniae* at 14%, and ESBL or AmpC-producing *Enterobacter* species at 32.2%. Resistance rates are higher in organisms cultured from patients in an ICU compared to patients not in an ICU. A recent surveillance trial of 48,440 Enterobacteriaceae isolates worldwide found three distinct groups of antimicrobial drugs in terms of spectrum of activity. The first group, carbapenems, had susceptibility rates of almost 100%. The second group, cefepime and amikacin, had susceptibility rates of 97.2–97.3%. The third group, which included ceftazidime, ceftriaxone, aztreonam, piperacillin-tazobactam, gentamicin, tobramycin, and the

fluoroquinolones, had susceptibility rates of 90%. Chromosomal cephalosporinases, including AmpC β -lactamase, are responsible for the high rate of resistance to ceftazidime. Plasmid-mediated penicillinases mediate resistance to ticarcillin, which frequently is associated with fluoroquinolone and aminoglycoside resistance. These data suggest that ESBL resistance affects β -lactam choices and other antimicrobial drugs.

Of interest, most nosocomial outbreaks are associated with relatively few bacterial clones, often with a single clone predominating. This finding implies poor infection control as a major cause of nosocomial outbreaks. Extended-spectrum β -lactamase resistance is stable once introduced into an ICU environment and can be transferred easily from one organism to another. Prior residency in a nursing home is a significant risk factor associated with ceftazidime resistance in *K. pneumoniae* and *E. coli*. Prior use of extended-spectrum cephalosporins, especially ceftazidime, also is an important risk factor. These data suggest that although these resistant pathogens may be commonly isolated from patients in the ICU, the organisms may not be nosocomially acquired.

Mortality rates are high (range of 42% to 100%) in patients treated with antibiotic drugs to which the ESBL-producing infecting organism is resistant. Successful treatment of patients with ESBL-producing gram-negative bacterial infection with cephalosporins, particularly in urinary tract infections, has been reported. However, cases of cephalosporin treatment failure in situations of known ESBL-production support the recommendation that any organism found to produce ESBL be regarded as resistant to all extended-spectrum β -lactam antibiotic drugs, regardless of in vitro MIC result. Infection control measures, as well as restriction of extended-spectrum cephalosporin use, have been variably effective in controlling outbreaks of ESBL-producing organisms.

Although the cephamycins remain active in vitro against ESBL-producing Enterobacteriaceae, there are limited clinical data supporting their use in treating serious infection due to these organisms. Clinical failure has been documented due to the emergence of resistance while a patient was receiving cephamycin therapy as a result of developing a porin-deficient mutant. Increasing numbers of ESBL-producing organisms express multiple β -lactamases, including AmpC-type enzymes that mediate resistance to cephamycins. Cefepime, a fourth-generation cephalosporin, is active against most ESBL-producing organisms; however, there are case reports of clinical failures of cefepime in treating infections due to ESBL-producing Enterobacteriaceae. Cefepime use also may select for ESBL-producing organisms, generating outbreaks of infection. Cefepime should not be considered first-line therapy for suspected ESBL-producing organisms, and if used, higher doses should be given in combination with other active drugs, such as aminoglycosides or fluoroquinolones.

Using β -lactam/ β -lactamase inhibitor combinations has been considered for treating infections due to ESBL-producing organisms. However, AmpC-mediated resistance is not affected by the presence of the β -lactamase inhibitors and will not respond to these changes in prescribing

patterns. Carbapenems routinely have activity against both ESBL- and AmpC β -lactamase-producing organisms, but empiric therapy with a carbapenem in all patients in an ICU or hospital ward can lead to carbapenem resistance among other bacteria. Knowledge of the extent of ESBL- and AmpC-mediated resistance in an institution is helpful in selecting appropriate empiric antibiotic therapy.

Efflux Systems

Efflux pumps are protein systems present in both gram-positive and gram-negative bacteria that expel toxic substances, including virtually all classes of currently used antibiotic drugs. Efflux pumps have been identified in most gram-negative bacteria, including the Enterobacteriaceae and *P. aeruginosa*. These efflux systems typically include three distinct proteins: an exporter protein located in the cytoplasmic membrane, a gated outer membrane protein located in the outer membrane, and a membrane fusion protein that links these two. The nomenclature for efflux pump systems is similar (e.g., MexA-MexB-OprM). Efflux pump genes may be part of an operon, with a regulatory gene controlling expression. Genes encoding for efflux systems can be found on plasmids, but most are chromosomal in gram-negative bacteria; the pumps normally play a physiological role in extruding toxic substances from the cell. Indeed, the intrinsic resistance of gram-negative bacteria to common antibiotic drugs, such as amoxicillin, tetracycline, or cefuroxime, can be overcome by genetic removal of constitutively produced efflux systems. Overexpression of efflux pumps causes resistance to previously active antibiotic drugs. Overexpression commonly results from mutations at the regulator gene, and results in resistance to antibiotic drugs of more than one class as well as some disinfectants and detergents. Table 1-3 lists four well-characterized efflux systems present in *P. aeruginosa*, and demonstrates substrate specificities for these multidrug efflux systems. In vitro studies suggest that biocide-resistant strains, which overexpress multidrug efflux systems and, thus, become resistant to multiple antibiotic drugs, can be selected in both *E. coli* and *P. aeruginosa*.

The understanding of efflux systems in gram-negative bacteria resistance is evolving, but no large-scale studies have evaluated the incidence or epidemiology of this resistance mechanism in nosocomial infection. Case reports of ciprofloxacin-associated efflux-mediated antibiotic resistance suggest that certain antibiotic drugs may have a greater selection pressure for overexpression of efflux systems.

Inhibitors of efflux pump function or production currently are being studied, but none seems to be a viable entity for clinical use for several years. Efflux pump inhibitors can lower the MIC of fluoroquinolones against both efflux-overexpressing *P. aeruginosa* and susceptible strains. The efflux inhibitor also can reduce the frequency of selecting fluoroquinolone-resistant strains. An intact efflux system may be necessary for mutations to occur in bacterial topoisomerase, the structural target of the fluoroquinolones. This association of efflux mechanism and mutations in genes encoding target site proteins may allow the use of an efflux pump inhibitor to expand the normal

Table 1-3. Antibiotic Drugs Affected by Four Well-characterized Efflux Systems in *Pseudomonas aeruginosa*^a

MexA-MexB-OprM	MexC-MexD-OprJ	MexE-MexF-OprN	MexX-MexY-OprM
Aztreonam	Cefepime	Chloramphenicol	Amikacin
Carbenicillin	Cefuroxime	Ciprofloxacin	Cefepime
Cefotaxime	Chloramphenicol	Clavulanate	Cefotaxime
Ceftazidime	Ciprofloxacin	Imipenem	Ciprofloxacin
Chloramphenicol	Erythromycin	Levofloxacin	Erythromycin
Ciprofloxacin	Levofloxacin	Norfloxacin	Gentamicin
Clavulanate	Nafcillin	Sulbactam	Levofloxacin
Levofloxacin	Norfloxacin	Trimethoprim	Tetracycline
Meropenem	Tetracycline		Tobramycin
Nafcillin	Trovafloxacin		
Norfloxacin			
Piperacillin			
Sulbactam			
Tetracycline			
Trimethoprim			

^aDefined as an 8-fold or greater increase or decrease in minimum inhibitory concentrations associated with overproduction or genetic deletion of the respective pump system.

Reprinted with permission from Pharmacotherapy. Aeschlimann JR. The role of multidrug efflux pumps in the antibiotic resistance of *Pseudomonas aeruginosa* and other gram-negative bacteria. *Pharmacotherapy* 2003;23:916–24.

activity of not only fluoroquinolones but other antibiotic drug classes.

Unfortunately, there are no standardized tests that clinical microbiology laboratories can perform to readily identify organisms that overexpress an efflux system. Preventing or managing potential clinical problems with efflux-mediated resistance must rely on proven techniques to mitigate any bacterial resistance. Optimizing antibiotic drug dosing to pharmacodynamic targets may improve clinical success and reduce the development of resistance. Combination antibiotic drug therapy also may decrease the likelihood of selecting an inherently resistant organism, particularly if drugs are selected that are substrates for different efflux pump systems.

Porin Channel Modification

Porins are major, water-filled, outer membrane proteins that allow diffusion of small polar molecules across the gram-negative membrane. Proteins that line these channels are called outer membrane proteins. Polar antibiotic drugs, including β -lactams, fluoroquinolones, and aminoglycosides, enter the periplasmic space through porin channels. Specificity of the outer membrane protein for the antibiotic drug is important. Mutations that produce either down-regulation of porin expression, or modification of the porin protein, can lead to antibiotic resistance. Examples include *P. aeruginosa* down-regulation of OprD expression which affects the activity of carbapenems, and organisms that fail to express OprF become resistant to fluoroquinolones.

Understanding the mechanisms of resistance allows for an educated choice for empiric therapy of infection. A team of pharmacists that practices direct patient care, makes formulary decisions, and prepares and dispenses antimicrobial dosage forms should recognize hospital-specific resistance patterns and their mechanisms,

and the team has a plan for drug use that takes this information into account.

Specific Organisms

All the nonfermentative gram-negative bacteria, and specifically *P. aeruginosa*, have intrinsic resistance mechanisms that make antibiotic drug therapy difficult. The outer membrane permeability for gram-negative bacteria is poor for hydrophilic antibiotic drugs, such as the β -lactams, but permeability may be 12–100-fold lower for *P. aeruginosa* and the other nonfermenter species compared to other enteric gram-negative bacilli. Efflux systems are known to be responsible for extensive intrinsic resistance among the nonfermentative gram-negative bacteria. The MexA-MexB-OprM system is critical for the intrinsic resistance of *P. aeruginosa*. Each nonfermenter contains an inducible, chromosomally encoded cephalosporinase. In *P. aeruginosa*, the enzyme is an AmpC-type β -lactamase that is induced on contact with sub-MICs of β -lactams, especially imipenem.

Pseudomonas aeruginosa

Table 1-4 lists the percentage of susceptible *P. aeruginosa* isolates to 10 common antipseudomonal drugs in the United States from 1998 to 2001. Multidrug resistance frequently is observed in *P. aeruginosa*, but no single mutation confers resistance to different antipseudomonal drugs. Sequential emergence of resistance is more likely because different antibiotic drugs are administered at different times after the development of resistance. Acquired resistance is associated with genetic changes that allow resistance mechanisms to be phenotypically expressed. β -Lactamase resistance usually is mediated by derepression of chromosomal β -lactamase. For *P. aeruginosa*, there appears to be synergy between the resistance mechanisms of low outer-membrane permeability and high, derepressed β -lactamase

Luzzaro F, Endimiani A, Docquier JD, et al. Prevalence and characterization of metallo- β -lactamases in clinical isolates of *Pseudomonas aeruginosa*. *Diagn Microbiol Infect Dis* 2004;48:131–5.

Table 1-4. 1998–2001 in vitro Susceptibilities to 10 Antimicrobial Drugs for Clinical Isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from non-ICU inpatients and ICU Patients in the United States

Drug	<i>Pseudomonas aeruginosa</i>		<i>Acinetobacter baumannii</i>	
	ICU	Non-ICU	ICU	Non-ICU
Amikacin	93.1%	92.0%	81.6%	78.8%
Cefepime	80.8%	82.2%	53.2%	51.2%
Ceftazidime	83.1%	86.6%	55.1%	48.5%
Ciprofloxacin	75.7%	73.2%	49.2%	41.0%
Gentamicin	77.1%	78.2%	53%	45.7%
Imipenem	80.3%	86.6%	96.6%	96.5%
Levofloxacin	72.5%	71.4%	55.1%	47.6%
Meropenem	78.7%	86.0%	91.7%	91.6%
Piperacillin-Tazobactam	91.2%	92.2%	n/a	61.1%
Ticarcillin-Clavulanate	73.8%	78.3%	n/a	71.2%

ICU = intensive care unit; n/a = data not available.

Reprinted with permission from the American Society of Microbiology. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Saham DF. Surveillance for antimicrobial susceptibility among clinical isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998 to 2001. *Antimicrob Agents Chemother* 2003;47:1681–8.

concentrations. Thus, cephalosporins, such as ceftazidime, which are not easily hydrolyzed by β -lactamase, will have MICs of 32-fold or more on mutational derepression of β -lactamases. Plasmid-mediated β -lactamases have been described in *P. aeruginosa*, but are not a major factor in clinical infection.

A recent study of ceftazidime restriction (44% reduction) in a large urban teaching hospital demonstrated a reduction in *P. aeruginosa* resistance to ceftazidime from 24% to 11.8% ($p < 0.001$), with a concomitant reduction in piperacillin resistance from 32.5% to 18.5% ($p < 0.001$). Less severe restriction in imipenem use (18% reduction) produced a decline in imipenem resistance from 20.5% to 12.3% ($p < 0.001$). Of interest, aztreonam resistance declined from 29.5% to 16.5% ($p < 0.001$) despite a 57% increase in use. These data suggest that an antimicrobial restriction program targeted at the major drivers of pseudomonal resistance, such as ceftazidime and imipenem, may result in reduced resistance of *P. aeruginosa* to these and other β -lactams.

National Nosocomial Infection Surveillance system data for 2002 reported that imipenem-resistance in *P. aeruginosa* nosocomial infection was 23.3%, a 32% increase over rates during the 1997–2001 period. Imipenem MICs for *P. aeruginosa* are independent of derepression of the chromosomal AmpC β -lactamase. *Pseudomonas aeruginosa* overexpression of efflux systems, such as the MexA-MexB-OprM, does not affect imipenem MICs. Imipenem readily selects resistant *P. aeruginosa* mutants that lack the OprD porin protein. This porin protein facilitates the permeability of the carbapenems but not other

β -lactams. Its loss raises imipenem MICs (normally 1–2 mcg/ml) to concentrations above the Clinical and Laboratory Standards Institute breakpoint of 16 mcg/ml, thus producing clinical resistance. In an OprD porin-deficient *P. aeruginosa* strain, stably derepressed production of carbapenamase leads to even higher levels of resistance to imipenem. Meropenem is significantly more potent against *P. aeruginosa* than imipenem, with typical MICs of 0.12–0.5 mcg/ml. Unlike imipenem, meropenem is affected by MexA-MexB-OprM up-regulation. It also is affected by the loss of OprD, but although elevated, meropenem MICs against *P. aeruginosa* with either of these resistance mechanisms remain well below the Clinical and Laboratory Standards Institute breakpoint of 16 mcg/ml (2–4 mcg/ml). However, organisms expressing both OprD loss and efflux resistance mechanisms will produce clinically significant meropenem resistance. Although no formal studies of meropenem resistance emerging during therapy have been done, there are far fewer case reports of clinical resistance than for imipenem, even after several years of use.

Loss of the OprD porin protein mediates the majority of carbapenem resistance. At least 50% of the *P. aeruginosa* isolates treated with imipenem for more than 7 days will show OprD loss. The presence of acquired metallo- β -lactamases produces both imipenem and meropenem resistance in *P. aeruginosa*. Although uncommon (less than 1%), metallo- β -lactamase-producing clinical strains of *P. aeruginosa* have been reported worldwide. Metallo- β -lactamases are not inhibited by the current β -lactamase inhibitors and effectively hydrolyze all known β -lactams.

Fluoroquinolone resistance in *P. aeruginosa* can arise from various resistance mechanisms. Although target site modification produced by mutation of the deoxyribonucleic acid gyrase- or topoisomerase-encoding genes does cause elevations in the MIC for fluoroquinolones, reductions in porin proteins and reduced bacterial accumulation of drug produce the greatest extent of fluoroquinolone resistance in most gram-negative bacteria. Ciprofloxacin activity against *P. aeruginosa* decreased nationally from 89% in 1990–1993 to 68% in 2000. This decline in ciprofloxacin activity correlates with a more than 2.5-fold increase in fluoroquinolone prescribing over the past 10 years. A similar trend was observed for susceptibility of gram-negative rods to ciprofloxacin, with a 13% decrease in susceptibility nationwide described over 6 years, from 89% in 1990–1993 to 76% in 2000. Cross-resistance between ciprofloxacin and other drugs, such as gentamicin, ceftazidime, imipenem, and amikacin, was observed for *P. aeruginosa*, *Enterobacter* species, and *K. pneumoniae*. Significant declines in susceptibility to the fluoroquinolones were observed over 9 years (1991–2000) for *P. aeruginosa* (-25.1%), *P. mirabilis* (-11.9%), *Enterobacter cloacae* (-6.6%), *E. coli* (-6.8%), and *S. maltophilia* (-17.4%) in a series of hospitals. Fluoroquinolone resistance in

Hancock RE. Resistance mechanisms in *Pseudomonas aeruginosa* and other nonfermentative gram-negative bacteria. *Clin Infect Dis* 1998;27(suppl):S93–9.

Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991–2000. *Clin Infect Dis* 2003;37:1643–48.

P. aeruginosa was positively correlated with fluoroquinolone use in the study institutions.

Multidrug resistance in *P. aeruginosa* that occurs as a result of fluoroquinolone exposure could be partly because of multidrug efflux pumps. Fluoroquinolones readily select in vitro mutants of *P. aeruginosa* that constitutively overproduce one or more Mex-Opr efflux system. There is a high probability of selecting multidrug efflux-overproducing mutants during fluoroquinolone monotherapy of *P. aeruginosa*, especially if inadequate dosages are provided.

***Acinetobacter* Species**

Nosocomial infection with *Acinetobacter baumannii* is particularly prone to inadequate empiric therapy because most strains are resistant to multiple antibiotic drugs (Table 1-4). The number of isolates and reports of hospital outbreaks over the past 6–10 years has steadily rose, particularly in ICUs. These outbreaks frequently are associated with multiple antibiotic drug resistance. Although imipenem and meropenem continue to exhibit potent in vitro activity against *A. baumannii*, several recent reports of hospital outbreaks have documented the spread of imipenem-resistant strains.

Carbapenem resistance in *A. baumannii* may be due to a multiple resistance mechanism. Diminished porin expression, along with increased AmpC β -lactamase activity may produce synergistic carbapenem-resistance. β -Lactamase expression that produces weak hydrolytic activity of carbapenems may contribute to resistance in porin-deficient isolates of *Acinetobacter*. Although altered penicillin-binding proteins and efflux pump expression also could participate in *Acinetobacter* resistance to the carbapenems, there are insufficient data to conclusively describe their role.

Several independent risk factors contribute to the development of a multidrug-resistant *A. baumannii* infection. Those risk factors include the length of time in the hospital before development of an *Acinetobacter* infection, age older than 65 years, ICU stay, and prior antibiotic drug therapy (particularly third-generation cephalosporins or imipenem). Other risks include endotracheal intubation or tracheostomy, surgery, urinary catheters, or intravascular catheters.

There is controversy about whether an *Acinetobacter* infection adversely affects patient outcomes, particularly in the ICU. These data were reviewed to evaluate the outcome and attributable mortality in critically ill patients with nosocomial bacteria involving *A. baumannii*. Using a retrospective case-control methodology, investigators could not demonstrate an adverse effect associated with *Acinetobacter* infection on outcome in patients in the ICU after controlling for the severity of underlying illnesses. Other researchers have found similar results in a case-control study of *A. baumannii* VAP.

In practice, colonization of endotracheal tubes, urinary catheters, and other indwelling devices with *Acinetobacter* species is common in many ICUs. Most infections associated with *Acinetobacter* colonization resolve after withdrawing the device, even in the absence of antimicrobial therapy. In many patients in the ICU, isolation of *A. baumannii* may be a surrogate marker for disease severity, but is associated with little clinical consequence alone. Nonetheless, the clinician is faced with a challenging therapeutic decision when *Acinetobacter* is cultured from a patient. Antibiotic drug treatment of *Acinetobacter* infection is limited. Carbapenems typically retain activity against most isolates, but imipenem-resistant strains are increasingly being identified. Colistin (polymyxin E) is highly active against these multidrug-resistant strains. Colistin originally was used in the 1960s and 1970s, but its use was largely abandoned because of concerns about nephrotoxicity and neurotoxicity. Recently, colistin has been effective in treating multidrug-resistant *P. aeruginosa* and *A. baumannii* pneumonia and bacteremia. Colistin was as effective as imipenem in managing *A. baumannii* VAP in a small open-label trial. Colistin dosing in patients with normal renal function is 2.5–5.0 mg/kg/day in three divided dosages. The drug is predominantly renally eliminated, and dosage adjustment is necessary in patients with decreased creatinine clearance.

A recent report suggested that aerosolized ampicillin-sulbactam 3 g every 8 hours in combination with systemic administration of ampicillin-sulbactam was more effective than intravenous therapy alone in reducing bacterial counts in 20 intubated and mechanically ventilated patients who had multidrug-resistant *A. baumannii* cultured from bronchial secretions. Although the patients did not demonstrate infection from the organism, aerosolization of ampicillin-sulbactam may represent an effective means of radically decreasing the colonization level of the upper respiratory tract by multidrug-resistant *Acinetobacter* species. This may reduce the development of VAP in this at-risk population.

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia is a nonfermentative, gram-negative opportunistic pathogen in nosocomial infection. It primarily affects immunocompromised patients, including patients in the ICU. Its pathogenicity is thought to be limited, but there are many reports of bacteremia and other serious infection caused by the organism. *Stenotrophomonas maltophilia* infection has been associated with an increased length of ICU stay and extended duration of mechanical ventilation. Increased mortality has been reported in patients with VAP, and this may be due in part to inadequate selection of empiric antimicrobial therapy. *Stenotrophomonas maltophilia* is difficult to treat and eradicate because isolates frequently are resistant to broad-spectrum antibiotic drugs, including the carbapenems. Trimethoprim-sulfamethoxazole and

Blot S, Vandewoude K, Colardyn F. Nosocomial bacteremia involving *Acinetobacter baumannii* in critically ill patients: a matched cohort study. *Intensive Care Med* 2003;29:471–5.

Garnacho J, Sole-Violan J, Sa-Borges M, Diaz E, Rello J. Clinical impact of pneumonia caused by *Acinetobacter baumannii* in intubated patients: a matched cohort study. *Crit Care Med* 2003;31:2478–82.

ticarcillin-clavulanate are considered top choices for treating an *S. maltophilia* infection, but routine testing of isolates for susceptibility to these drugs is not performed in all microbiology laboratories.

Escherichia coli

The increasing use of the fluoroquinolones has led to quinolone-resistant *E. coli*. One report from an individual institution found that from 1996 to 2000, 297 cases of urinary tract infection due to quinolone-resistant *E. coli* were observed; 218 episodes (73.5%) were community acquired. The incidence of quinolone-resistant *E. coli* urinary tract infections increased steadily from 14.4% to 21.3% during the 5-year period. Significant differences in susceptibility to various antibiotic drugs have been observed between quinolone-resistant *E. coli* and fluoroquinolone-susceptible strains of *E. coli*. The multidrug resistance rate of quinolone-resistant *E. coli* was much higher (38.3%) than those of fluoroquinolone-susceptible isolates (18.8%).

Risk factors for quinolone-resistant *E. coli* include recent fluoroquinolone use, recent therapy with other antimicrobial drugs (such as aminoglycosides), residence in a long-term care facility, urinary tract abnormalities, and age older than 65 years. The impact on outcome of quinolone-resistant *E. coli* is undetermined, but successful treatment of *E. coli* urinary tract infections may be dependent on fluoroquinolone resistance. Thirty-day mortality has been higher in patients with quinolone-resistant *E. coli* urinary tract infections.

The development of fluoroquinolone resistance in *E. coli* may be associated with mutations in regulatory genes that lead to increased multidrug efflux. Genomic diversity has been found among both community and nosocomial strains. The increased frequency of quinolone-resistant *E. coli* may not be due to transmission of resistant strains, but may result from the selection of resistant strains from the endogenous flora of patients.

Efforts should be directed at recognizing and modifying risk factors to curb the rise in fluoroquinolone resistance and preserve the use of these drugs for treating common nosocomial gram-negative infections. Prudent use of fluoroquinolones, especially in patients with urinary tract abnormalities, is probably the best way to avoid an increase in the incidence of quinolone-resistant *E. coli* infections; however, further studies on interventions with restricted quinolone use are necessary to demonstrate the effectiveness and safety of this strategy.

Pharmacotherapy

Pharmaceutical Care: Optimizing Outcome

The ultimate goals in managing nosocomial gram-negative infections are to prevent infection in noninfected patients and to completely cure patients who become infected. Cure typically describes not only eradication of the causative pathogen, but also resolving the signs and symptoms associated with infection. In general, antimicrobial drugs only accomplish the former. Pharmacotherapy of infection must be based not only on organism eradication, but it also must be directed to avoid

potential adverse events and be economically sound for the institution. In addition to pharmacotherapy, there are other nondrug interventions that play a key role in managing nosocomial gram-negative infections. Pharmacists are best suited to provide key information regarding pharmacology, drug use and safety, and pharmacoconomics to prescribers and other clinicians to optimize the pharmacotherapy of infection.

Factors Guiding Antimicrobial Therapy Strategies for Appropriate use

Many factors must be considered when deciding on therapy for a patient with a suspected or documented nosocomial gram-negative infection. These factors include the most likely pathogens for the suspected infection source, local susceptibility patterns, current or prior antimicrobial therapy in the patient, available formulary drugs, their efficacy and side effect profiles, pharmacodynamics and pharmacokinetics, and most important, the clinical condition of the patient. Other factors related to the antimicrobial regimen itself include timing of therapy, potential drug combinations, and their dosage and administration schedule. Timing involves not only prompt initiation of therapy, but also the appropriate treatment duration. Initial empiric regimens may require alteration based on the clinical response of the patient, the culture and susceptibility report, or the desire to de-escalate therapy in a patient who is responding well.

Dosing

Ineffective antimicrobial dosing is a common but poorly recognized cause of treatment failure, and is clearly associated with an increased probability of resistance emerging during therapy. Pharmacist-based individualized dosing programs have existed in hospitals since clinical pharmacy originated. Most programs are focused on pharmacokinetic analysis of serum concentrations, and other surrogate markers. More recently, the importance of pharmacodynamics in addition to pharmacokinetics has been emphasized.

Manipulation of drug dosing based on pharmacodynamic principles is a method to seek maximum bacterial killing and minimize bacterial resistance. β -Lactams, monobactams, and carbapenems exhibit concentration-independent killing; the principle for these drugs is to maximize the time the serum drug concentration exceeds the MIC of the causative pathogen. For most gram-negative bacteria, maintaining serum antibiotic concentrations above the MIC for 60–70% of the dosing interval predicts maximum survival in animal models of infection. Continuous infusion of concentration-independent antibiotic drugs maximizes time above the MIC. Numerous in vitro investigations and clinical trials evaluating continuous infusion of ceftazidime, cefepime, piperacillin-tazobactam, and meropenem have been published (Table 1-5). Stability issues, particularly with carbapenems, must be considered when using continuous infusion methods.

Pharmacodynamic principles also have been studied for antibiotic drugs that are concentration-dependent in their bacterial killing, such as aminoglycosides and fluoroquinolones. Aminoglycosides have been studied

Table 1-5. Selected Studies of Continuous Infusion Antibiotic Drug Dosing Strategies

Reference	Drug and Dosage Regimens	Findings/Outcomes
Boselli E, et al. Crit Care Med 2003;31:2102–6.	Cefepime CI 4 g over 24 hours	4 g/day provides constant serum and ELF concentrations greater than the MICs of most susceptible nosocomial pathogens
Grant EM, et al. Pharmacotherapy 2002;22:471–83.	Piperacillin-tazobactam CI variable dose, depending on estimated CrCl and type of infection ^a versus II	Clinical and microbiological success rates trended in favor of CI; days to normalization of fever less in CI group; total cost of therapy less in CI group
McNabb JJ, et al. Pharmacotherapy 2001;21:549–55.	Ceftazidime CI 3 g/day versus II 2 g 3 times/day plus tobramycin	Clinical success rates, adverse events, and length of stay were similar between groups. Cost was significantly lower in the CI group
Hanes S, et al. Am J Surg 2000;179:436–40.	Ceftazidime CI 60 mg/kg/day versus II 2 g 3 times/day	Clinical success similar between groups. Percentage of time serum concentrations exceeded MICs similar between groups
Thalhammer F, et al. J Antimicrob Chemother 1999;43:523–7.	Meropenem CI 3 g/day versus II 2 g every 8 hours, crossover design	PK and PD analysis only. The PKs and the percentage of time serum concentrations exceeded MICs for common pathogens were similar between groups

^aDose ranged from piperacillin 8 g plus tazobactam 1 g to piperacillin 12 g plus tazobactam 1.5 g/day.

CI = continuous infusion; CrCl = creatinine clearance; ELF = epithelial lining fluid; II = intermittent infusion; MIC = minimum inhibitory concentration; PD = pharmacodynamic; PK = pharmacokinetic.

extensively when given in large doses at extended intervals compared to conventional multiple daily-dose regimens. Achieving an aminoglycoside serum maximum concentration of drug-MIC ratio of greater than or equal to 10 demonstrates a 90% probability of temperature and white blood cell count resolution by day 7 of therapy. Aminoglycosides also demonstrate a concentration-dependent postantibiotic effect that allows for the serum concentration to fall below the MIC of the pathogen for an extended portion of the dosing interval, apparently without impairing antimicrobial activity. Reports of extended interval dosing in VAP, bacteremia, and urinary tract infections have shown more rapid bacterial eradication, shorter length of stay, and lower mortality compared to conventional dosing. Nephrotoxicity and oto-vestibulotoxicity have been similar between these two dosing strategies, or possibly slightly less in favor of the extended-interval dosing.

Although the pharmacodynamic properties of fluoroquinolones are similar to those of aminoglycosides, the principal target has been maximizing the area under the concentration-time curve-MIC ratio. A study with ciprofloxacin in gram-negative nosocomial infection (primarily pneumonia) demonstrated a clinical cure rate of 82% for area under the concentration-time curve-MIC greater than 125 (median 234), and 42% for area under the concentration-time curve-MIC less than 125 (median 111). Organism eradication rates were 82% for area under the concentration-time curve-MIC ratio greater than 125 (median 320) and 26% for area under the concentration-time curve-MIC ratio less than 125 (median 90). Time to bacterial eradication was greater than 32 days for

area under the concentration-time curve-MIC ratio less than 125, 6.6 days for area under the concentration-time curve-MIC ratio 125–250, and 1.9 days for area under the concentration-time curve-MIC ratio greater than 250. These data have largely provided the support for targeting area under the concentration-time curve-MIC values of 125–250 when using fluoroquinolone therapy to treat gram-negative infections.

Patients with nosocomial infection, particularly the critically ill, may have pharmacokinetic alterations with one or more antimicrobial drugs. Pharmacokinetic changes in this population include larger volumes of distribution secondary to volume overload, decreased serum protein concentrations leading to decreased protein binding, decreased metabolism and clearance due to organ dysfunction or hypoperfusion, or increased metabolism and clearance due to a hypermetabolic state. Subsequent alterations in elimination half-life may be observed due to changes in clearance and volume of distribution. Table 1-6 represents a selection of the published studies of altered pharmacokinetics in critical illness. Pharmacists should be cognizant of altered pharmacokinetics from disease and be able to make appropriate recommendations for dosing and administration schedules.

Guidelines

The use of guidelines, practice parameters, and other clinical pathways and protocols is associated with more appropriate drug use, improved patient outcomes, fewer adverse events and errors, and better resource use for many disease states. Guidelines have been effective in managing nosocomial infection. A recent study documented one

Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob Agents Chemother* 1999;43:623–9.

Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993;37:1073–81.

institution's experience with a clinical protocol for managing VAP. The protocol was directed at selecting adequate empiric therapy for patients with VAP and reducing unnecessary antimicrobial drug use. Investigators prospectively measured outcome variables in 50 patients before implementing the guidelines, and 52 patients after implementation. Protocol-driven prescribing was significantly more effective in selecting adequate empiric therapy (94.2% vs. 48%). Protocol use produced a significant reduction in the number of days of treatment (8.6 vs. 14.8), and significantly lowered the incidence of recurrent VAP (7.7% vs. 24%) compared to the control period. Hospital length of stay, ICU length of stay, and mortality were not different between the groups.

Therapy

Strategies for preventing nosocomial gram-negative infections vary depending on the institution, infection type, and the patient. Indwelling devices, such as intravascular catheters, indwelling urinary catheters, gastric and jejunal tubes, surgical drains, endotracheal or tracheostomy tubes, thoracostomy tubes, indwelling brain catheters and monitors, and rectal tubes, are a major risk factor for developing infections in hospitalized patients. All of these devices can increase the nosocomial infection risk. Typically, the risk is increased for the anatomic location in which the device resides, such as indwelling urinary catheters with urinary tract infections. However, some devices may be associated with multiple nosocomial infection sources, such as endotracheal tubes with pneumonia and sinusitis. Minimizing the use of these devices may decrease a patient's chance of developing a nosocomial infection, but the risk of device use must be weighed against its potential benefits.

Bloodstream Infections

Patients with a central venous catheter are at risk for exit-site infection as well as bacteremia. Most infections related to central venous catheterization are due to gram-positive organisms, specifically coagulase-negative staphylococci and *Staphylococcus aureus*. Intravascular catheters are uncommon causes of nosocomial bloodstream infections. Gram-negative bacteremia usually is the result of metastatic infection usually arising from the lungs, abdomen, or urinary tract. Nosocomial sepsis carries a high incidence of morbidity and mortality, and frequently is associated with bacteremia.

Although randomized, controlled data are not available, the importance of prompt initiation of antimicrobial drug therapy is supported by consensus recommendations on managing sepsis. Empiric therapy is guided by likely pathogens, based on the suspected infection source. Initial empiric therapy should be broad and include drugs that are active against both gram-positive and gram-negative pathogens. Specific attention should be paid to the local susceptibility patterns in choosing empiric therapy. Intravenous administration should be used, and maximal dosing of antibiotic drugs used to rapidly eradicate the pathogen. For a nonpseudomonal bloodstream infection, appropriate monotherapy is as effective as appropriate combination therapy in organism eradication and patient survival. Data from a systematic review of β -lactam monotherapy versus β -lactam-aminoglycoside combination therapy suggest no advantage to combination therapy in patients with gram-negative infection. However, administering combinations of antibiotic drugs that are active against gram-negative pathogens may reduce the likelihood of inappropriate therapy due to bacterial resistance. Antibiotic drug combinations such as aminoglycosides combined with third-generation cephalosporins demonstrate synergy in vitro, but they have

Table 1-6. Selected Studies Evaluating Altered Pharmacokinetics in Critically Ill Patients

Reference	Drug and Dosage Regimen	Findings
Joynt GM, et al. J Antimicrob Chemother 2001;47:421–9.	Ceftriaxone 2 g once daily	The Cl increased 100%, V_d increased 90%, and $t_{1/2}$ was similar compared to healthy volunteers (historical cohort)
Hanes S, et al. Am J Surg 2000;179:436–40.	Ceftazidime continuous infusion and intermittent infusion	Pharmacokinetics in both dosing regimens were similar. The Cl and V_d about 50% higher in critically ill compared with healthy volunteers
Lipman J, et al. Antimicrob Agents Chemother 1999;43:2559–61.	Cefepime 2 g every 12 hours	80% of patients had plasma trough concentrations below the MIC_{50} for <i>Pseudomonas aeruginosa</i> . Computer modeling predicted adequate concentrations with shorter dosage intervals and CI
Gomez CM, et al. Antimicrob Agents Chemother 1999;43:1798–802.	Ceftazidime 2 g 3 times/day	The V_d and $t_{1/2}$ significantly higher than in healthy controls. The Cl and AUC were not different
McKindley DS, et al. Pharmacotherapy 1996;16:924–31.	Aztreonam 2 g every 8 hours; imipenem 500 mg every 6 hours	The V_d for aztreonam and imipenem was significantly larger than in historical controls. The $t_{1/2}$ was significantly longer for aztreonam than historical controls, but not imipenem. The Cl was not significantly different between any comparisons

AUC = area under the concentration-time curve; CI = continuous infusion; Cl = clearance; MIC_{50} = minimum inhibitory concentration at which 50% of isolates are inhibited; $t_{1/2}$ = elimination half-life; V_d = volume of distribution.

not been more effective than monotherapy in clinical investigations.

Most clinicians treat *P. aeruginosa* infections in the lung or bloodstream with combination antibiotic drug therapy. Data supporting this practice are limited. One retrospective review of 115 patients treated with either monotherapy or combination therapy for *P. aeruginosa* bacteremia evaluated early mortality (before receipt of the culture and susceptibility data) and late mortality (after receipt of the culture and susceptibility data out to day 30) for patients who received empiric/adequate monotherapy, empiric/adequate combination therapy, or inadequate empiric therapy, and definitive/adequate monotherapy, definitive/adequate combination therapy, or inadequate definitive therapy. There was no difference in early mortality among the treatment groups. Using multivariate analysis, late mortality was significantly higher in patients who had received empiric/adequate monotherapy or inadequate therapy compared to those who had received empiric/adequate combination therapy. Although late mortality in the definitive/inadequate therapy was significantly higher than in the definitive/adequate therapy groups, late mortality in the definitive/adequate monotherapy and definitive/adequate combination therapy groups was similar. An earlier retrospective analysis supports the use of combination therapy for *P. aeruginosa* bacteremia. Effective empiric antibiotic drug combinations may include antipseudomonal penicillins, cephalosporins, carbapenems, or aztreonam combined with fluoroquinolones or aminoglycosides.

Pneumonia

The dominant risk factor for nosocomial pneumonia is endotracheal intubation and mechanical ventilation. In addition, most mechanically ventilated patients are critically ill, further increasing their risk for nosocomial infections. The non-pharmacological approach to preventing nosocomial pneumonia is primarily accomplished with appropriate and aggressive pulmonary hygiene care. One of the most important parts of this care is endotracheal suctioning, as these patients are unable to clear their respiratory secretions on their own through coughing. Other important non-pharmacological interventions include extubation as early as possible, limiting contamination of the ventilatory circuitry (tubing), appropriate patient positioning (raised 30 degrees), and chest percussion and postural drainage.

Pharmacological pneumonia prevention strategies primarily have targeted two areas: maintaining or enhancing the clearance of respiratory secretions, and preventing colonization and subsequent infection of the respiratory tract. Inhaled β -agonists such as albuterol are used to clear secretions through bronchodilation, regardless of the presence of reactive airway disease. Inhaled anticholinergic drugs may be added to β -agonist therapy to enhance large airway bronchodilation. Ipratropium is used almost exclusively as the inhaled anticholinergic of choice due to its proven efficacy in the critically ill, and its lower incidence of side effects compared to other anticholinergic drugs. Tiotropium, a new anticholinergic drug for inhaled use, may be more convenient to administer (once daily

dosing) than ipratropium (4 times/day dosing), but its use in the acutely ill population has not been tested. *N*-acetylcysteine also is used in certain patients with thick secretions and mucous plugging, the goal being improved clearance by thinning the viscosity of the secretions and loosening mucous plugs.

Pharmacological prophylaxis of stress-related mucosal damage and bleeding may play a role in nosocomial pneumonia. Although controversial, evidence exists that using drugs such as proton-pump inhibitors and histamine-2 antagonists increases gastric pH, thereby allowing for bacterial overgrowth of organisms and increasing the risk of nosocomial aspiration pneumonia. Gram-negative pathogens associated with aspiration are mainly Enterobacteriaceae. Some clinicians advocate such drugs as sucralfate, that do not significantly raise gastric pH, for preventing stress-related mucosal damage.

Ventilator-associated Pneumonia

Gram-negative bacteria commonly encountered in VAP are shown in Table 1-2. Empiric therapy should include broad-spectrum drugs as early as VAP is recognized. Initiating antimicrobial drug therapy more than 24 hours after diagnosis is associated with increased morbidity, mortality, length of stay, and cost. Gram-negative bacterial pathogens in early VAP (occurring within 48–72 hours after hospital admission) include *Haemophilus influenzae*, *E. coli*, *Klebsiella* species, *Proteus* species, and *Serratia marcescens*. If early VAP is suspected, empiric therapy should include a nonpseudomonal second- or third-generation cephalosporin, a β -lactam/ β -lactamase inhibitor combination, or advanced-generation fluoroquinolone. Late VAP (occurring more than 48–72 hours after hospital admission) pathogens include *P. aeruginosa*, *A. baumannii*, *E. coli*, *Klebsiella* species, *Proteus* species, and *S. marcescens*. *Staphylococcus aureus* also is a common pathogen in VAP, requiring broader-spectrum antibiotic coverage. A recent consensus conference established recommendations for treating late VAP, including an antipseudomonal cephalosporin or penicillin, an antipseudomonal β -lactam/ β -lactamase inhibitor combination, or a carbapenem as monotherapy. Fluoroquinolones cannot be used for monotherapy due to the significant increase in resistance observed with *P. aeruginosa*. Ciprofloxacin and levofloxacin have been effective for empiric treatment of nosocomial pneumonia when used in combination with other antipseudomonal therapy. Although two sets of broad-based guidelines have been published, neither are of significant value when choosing antimicrobial therapy for treating VAP. The American Thoracic Society guidelines were published almost 10 years ago, and their relevance to resistance patterns and current antimicrobial use is limited. A much more recent consensus paper from an expert panel was published in 2001. However, this panel of experts from Europe and Latin America stated, "... no consensus was reached regarding choices of antimicrobial agents or the optimal duration of therapy." and "All the peers agreed that the pathogens causing VAP and multiresistance patterns in their ICUs were substantially different than those ... in the United States."

Table 1-7. Studies of Monotherapy Versus Combination Therapy for Gram-negative Nosocomial Pneumonia

Monotherapy	Success Rate	Combination	Success Rate	Reference
Aztreonam	92% (24/26)	Tobramycin plus various	50% (7/14)	Schentag JJ, et al. Am J Med 1985;78:34–41.
Cefoperazone	87% (45/52)	Clindamycin or Cefazolin plus gentamicin	72% (44/61)	Mangi RJ, et al. Am J Med 1988;84:68–74.
Ceftazidime	88% (15/17)	Tobramycin plus ticarcillin	83% (15/18)	Rapp R, et al. Pharmacotherapy 1984;4:211–15.
Ceftazidime	88% (21/24)	Tobramycin plus cefazolin	92% (24/26)	Mandell LA, et al. J Antimicrob Chemother 1983;12(suppl A):9–20.
Imipenem	86% (38/44)	Cefotaxime plus amikacin	76% (34/45)	Mouton JW, et al. Presse Med 1990;19:607–12.
Cefoperazone or Ceftazidime plus gentamicin	56% (22/39)	Cefoperazone or ceftazidime	31% (22/70)	Croce MA, et al. J Trauma 1993;35:303–39.
Cefotaxime	79% (217/275)	Various	71% (193/273)	Fernandez-Guerrero M, et al. Infection 1991;19(suppl 6):S320–5.
Ceftazidime	58% (99/159)	Ceftriaxone plus tobramycin	46% (64/138)	Rubinstein E, et al. Clin Infect Dis 1995;20:1217–28.
Ceftazidime	93% (12/13)	Ticarcillin plus tobramycin	76% (9/11)	Cone LA, et al. Antimicrob Agents Chemother 1985;28:33–6.
Total	76% (493/649)	Total	63% (412/656)	

Many studies have compared antibiotic monotherapy to combination therapy for managing VAP or nosocomial pneumonia (Table 1-7). Early-onset pneumonia usually is associated with *Streptococcus pneumoniae*, *H. influenzae*, enteric gram-negative bacilli, or *S. aureus*. Late-onset pneumonia, occurring more than 7 days after admission, or antibiotic use before the development of pneumonia, are associated with *Acinetobacter* species, *P. aeruginosa*, and multiresistant organisms. Multidrug resistance in pneumonia pathogens is almost exclusively associated with either prolonged duration of stay in the institution or prior antibiotic drug therapy. Patients who receive antibiotic drug therapy as an outpatient, or patients who are residents in nursing homes or other institutional facilities also are at risk for multidrug resistance. Therefore, patients who are not at risk for multidrug resistance who develop early-onset nosocomial pneumonia or VAP can be adequately treated with monotherapy. These therapies could include β -lactam/ β -lactamase inhibitor combinations, non-antipseudomonal third-generation cephalosporins, second-generation cephalosporins, fluoroquinolones, or carbapenems. The data from trials of antibiotic monotherapy versus combination therapy do not suggest a benefit compared to combination therapy (Table 1-7). Many of these trials were performed before the current state of multidrug resistance began. Patients with severe infections caused by *P. aeruginosa*, multidrug resistant *Klebsiella* species, or *Acinetobacter* species may be better treated with antibiotic drug combinations; however, there are insufficient data to support this as a level I recommendation. In vitro studies predict synergy against *P. aeruginosa* and other

nonfermentors for β -lactam plus aminoglycoside combinations. In vitro synergy typically is not observed against *P. aeruginosa* for antipseudomonal β -lactam plus fluoroquinolone combinations, although there may be an additive effect. There are few data that demonstrate synergy for these combinations in vivo.

Modifying empiric therapy based on clinical response of the patient and culture and susceptibility reports should be considered early in therapy. Patients failing therapy, even when the microbiological data support the current regimen, require changes in therapy. Some resistance mechanisms are inducible; thus, microbiological, phenotypic expression of the resistance may not be observed until therapy has been initiated. For patients who respond to initial empiric therapy, de-escalation of the antimicrobial regimen to focus antibiotic drug therapy specifically at the causative pathogen should be attempted. De-escalation is desirable because it can decrease antimicrobial pressure on the development of resistance, adverse drug events, and cost.

Therapy duration for nosocomial pneumonia has not been adequately defined. Most clinical studies have evaluated 10–14 days of antibiotic drugs. This principle was largely guided by early data on the treatment of *Streptococcus pyogenes* pharyngitis. Two recent studies of nosocomial pneumonia have challenged this duration. Investigators randomized all patients in an ICU with an equivocal diagnosis of VAP based on the Clinical Pulmonary Infection Score to either ciprofloxacin 400 mg intravenously every 8 hours for 3 days, or therapy left to the discretion of the attending physician (the control group). At the end of 3 days of ciprofloxacin, Clinical Pulmonary

Infection Score was again performed, and patients with a continued equivocal diagnosis of pneumonia had their antibiotic drug discontinued (short-course treatment). Patients with a clear diagnosis of VAP were continued on antibiotic drugs at the physician's discretion. Patients who received short-course therapy had similar Clinical Pulmonary Infection Scores to the control group, but received 6.8 fewer days of antibiotic drugs ($p=0.0001$) costing 60% less than controls, stayed in the ICU 5.3 fewer days ($p=0.04$), had an 18% lower absolute mortality rate (13% vs. 31% for control [$p=0.06$]), and had a 24% absolute reduction in rates of superinfection and antibiotic resistance (14% vs. 38% for controls [$p=0.017$]).

A multicenter French study that compared 8 days versus 15 days of antimicrobial therapy for VAP found that patients treated for 8 days had similar mortality rates, rates of infection recurrence, rates of mechanical ventilation-free days, number of organ failure-free days, and length of ICU stay as patients receiving the longer duration of therapy. Only patients with VAP caused by nonfermenting gram-negative bacilli, including *P. aeruginosa*, had higher pulmonary infection recurrence with 8-day therapy compared to 15-day therapy; however, emergence of multidrug-resistant pathogens was less common in patients receiving 8-day regimen who experienced recurrence.

Recently, the success of an antibiotic discontinuation policy for clinically suspected VAP was reported. Patients were assigned to have the duration of antibiotic drug treatment for VAP determined by an antibiotic drug discontinuation policy (discontinuation group) or their treating physician teams (conventional group). Although the severity of illness and likelihood of VAP were similar between the groups, the duration of antibiotic drug treatment for VAP was statistically shorter among patients in the discontinuation group compared to patients in the conventional group (6.0 vs. 8.0 days; $p=0.001$). The occurrence of a secondary episode of VAP was not statistically different between these two groups. Hospital mortality and ICU length of stay also were statistically similar. These data support shorter courses of empiric antibiotic drug therapy for patients treated for suspected VAP.

Systems Management

Selective Decontamination of the Digestive Tract

Selective decontamination of the digestive tract for preventing nosocomial infections in patients in an ICU is not a new concept, having first been described more than 20 years ago. Effective selective decontamination of the digestive tract programs administer a broad-spectrum parenteral antimicrobial drug to prevent early nosocomial infections; administer oropharyngeal and enteral antimicrobials to prevent late nosocomial infections;

encourage handwashing and other routine infection control procedures; and survey cultures to monitor the therapy's effectiveness. The theory of this approach is that the aggressive use of parenteral and enteral antimicrobial drugs and surveillance cultures will prevent colonization of potential pathogens in a patient, decreasing the incidence of nosocomial infections from both gram-positive and gram-negative bacteria.

Although selective decontamination of the digestive tract is still controversial and not well accepted, one review comparing selective decontamination of the digestive tract to the more traditional approach of handwashing and restricting antimicrobial drug use has sparked new interest in the topic. The review pointed out that handwashing, restricting antimicrobial use, or the combination of the two has reduced mortality in patients in the ICU. The use of selective decontamination of the digestive tract has had beneficial effects both in morbidity and mortality in controlled studies and meta-analyses. However, practitioners are still hesitant to use selective decontamination of the digestive tract. Possible explanations for hesitance in using selective decontamination of the digestive tract include perceived lack of efficacy, concerns of potential impact on resistance, increased cost of administering selective decontamination of the digestive tract, and the labor-intensive nature of the selective decontamination of the digestive tract regimen. These concerns appear to be unfounded, as reasonable evidence exists to dispute each issue. Although there has not been a consensus for selective decontamination of the digestive tract to become the standard of care for patients who are acutely ill or in the ICU, it remains unclear why it is not used more often.

Antibiotic Restriction and Rotation Programs

System strategies to improve antimicrobial drug use range from relatively simple mechanisms such as formulary restrictions, to significantly complex programs such as antibiotic drug rotation schemes. Pharmacists have traditionally taken the lead in identifying, implementing, and monitoring drug use restriction policies. Pharmacists also play key roles in other antimicrobial stewardship initiatives in the hospital. Although almost all institutions have access to antibiotic drugs that are nonformulary, antibiotic restriction allows certain high-cost or second- and third-line antibiotic drugs to be targeted for restricted use. Use restrictions may be based on efficacy, criteria for use, resistance patterns, cost, or other factors. From a clinical standpoint, antimicrobial drugs usually are restricted because of documented or suspected overuse that may affect bacterial resistance. Because many gram-negative organisms are able to demonstrate resistance across varying antimicrobial classes, a restriction program may be implemented to limit resistance not only to the specific

Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162(2 Pt 1):505–11.

Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290:2588–98.

Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;125:1791–9.

Table 1-8. Studies on Antibiotic Rotation and Related Outcomes

Reference	Rotation Design	Outcomes
Gerding D, et al. Antimicrob Agents Chemother 1991;35:1284–90.	Gentamicin alternating with amikacin	Decreased gentamicin-resistant organisms after second cycling
Kollef M, et al. Am J Respir Crit Care Med 1997;156:1040–8.	Ceftazidime alternating with ciprofloxacin every 6 months	Decrease in VAP ^a and bacteremia ^b due to resistant gram-negative bacteria
Kollef M, et al. Crit Care Med 2000;28(10):3456.	Six-month rotation of empiric therapy for gram-negative infections: 1) ceftazidime, 2) ciprofloxacin, and 3) cefepime ^c	Decrease in inadequate antimicrobial therapy for gram-negative infections ^a and nosocomial infections overall ^b
Gruson D, et al. Am J Respir Crit Care Med 2000;162:837–43.	Monthly rotation of empiric antibiotic drugs for nosocomial pneumonia, with and without restriction of ceftazidime and ciprofloxacin	Lower incidence of VAP during rotation and restriction period
Raymond DP, et al. Crit Care Med 2001;29:1101–8.	Quarterly rotation of empiric therapy for VAP, peritonitis, and sepsis	Decrease in resistant gram-positive and gram-negative infections. Decrease in infection-related mortality. Rotation an independent predictor of survival

^ap<0.05.

^bp=NS.

^cCefepime only 5 months instead of 6 months because of manufacturer production shortage.

VAP = ventilator-associated pneumonia.

drugs being restricted, but also to other antimicrobial drugs. A recent study demonstrated the impact of such a program. Researchers at a large medical center with significant *P. aeruginosa* resistance to β -lactams implemented a pharmacist-facilitated, institution-wide antimicrobial restriction program. All orders for restricted antimicrobials (amikacin, azithromycin, aztreonam, ceftazidime, ciprofloxacin, clarithromycin, intravenous fluconazole, imipenem-cilastatin, levofloxacin, lipid-based amphotericin B, piperacillin-tazobactam, tobramycin, and vancomycin) were prospectively reviewed for appropriateness, and therapy was either continued or modified. Total antimicrobial drug use and resistance patterns before and after implementing the restriction program were compared. The largest decrease was in ceftazidime use, which declined by 44% during the 4 years after the restriction program began. Piperacillin use did not change significantly, carbapenem use declined slightly, and aztreonam use actually increased by 57%. *Pseudomonas aeruginosa* resistance to ceftazidime decreased from 24% to 11.8% (p<0.001). Similar significant declines in *P. aeruginosa* resistance were observed for piperacillin (32.5% vs. 18.5%; p<0.001), imipenem (20.5% vs. 12.3%; p<0.001), and aztreonam (29.5% vs. 16.5%; p<0.001). Other studies have shown similar results, in that changes in usage patterns of a single drug may be associated with resistance patterns for multiple drugs, even beyond the restricted drug's antimicrobial class.

The rationale for antibiotic drug rotation (cycling) in hospitals or the ICU is to limit bacterial exposure to certain antimicrobial drugs over a defined time period, to decrease

the emergence of resistance to those drugs, or delay the time it takes for organisms to become resistant to those drugs. It is futile to try to eliminate all antibiotic resistance, and the goal of antibiotic drug rotation is not to eliminate resistance, but to increase the time it takes for an organism to develop that resistance, and to minimize the level of resistance to any single drug. Rotating antibiotic drug classes also may remove the selective pressure from any one antibiotic drug class so that inherently resistant subpopulations of otherwise susceptible bacteria will diminish. Resistant subpopulations of otherwise susceptible bacteria typically are present in small percentages in a bacterial population. When that population is repeatedly exposed to the antibiotic drug to which the majority of the population is susceptible, the percentage of resistant clones within the population will increase. Theoretically, rotating antibiotic drugs can prevent that from happening.

Rotating antibiotic drug usage has been suggested for several years. Early studies focused mainly on resistance patterns, and any observable changes in these patterns associated with rotation programs. Follow-up studies to these early investigations have searched for an association between antibiotic drug rotation and patient outcomes, including mortality (Table 1-8). One of the first studies to demonstrate an effect on infection rates evaluated rates of VAP due to gram-negative bacilli in a medical ICU in a 7-year period. During the first 2 years, no protocol for antimicrobial drug use for VAP was used. For the next 5 years, a 1-month antibiotic drug rotation schedule was implemented. The frequency of VAP was significantly lower during the 5 years of the antibiotic rotation program

Regal RE, DePestel DD, VandenBussche HL. The effect of an antimicrobial restriction program on *Pseudomonas aeruginosa* resistance to β -lactams in a large teaching hospital. *Pharmacotherapy* 2003;23:618–24.

Gruson D, Hilbert G, Vargas F, et al. Strategy of antibiotic rotation: long-term effect on incidence and susceptibilities of gram-negative bacilli responsible for ventilator-associated pneumonia. *Crit Care Med* 2003;31:1908–14.

compared to the initial 2-year period. Gram-negative resistance rates remained unchanged.

A successful antibiotic drug rotation program was implemented in a surgical ICU for patients who developed pneumonia, peritonitis, or sepsis. The 1-year period of antibiotic drug rotation was compared to the previous 1-year period in which antibiotic drug use was at the discretion of the attending physician. Antibiotic drug rotation occurred quarterly and varied with the infection type, pneumonia, peritonitis, or sepsis. Fluoroquinolones, cephalosporins, carbapenems, and β -lactam/ β -lactamase inhibitor combinations were involved in the rotation. Infection-related mortality decreased significantly during the protocol-driven period from 56.4% to 34.8% ($p=0.035$). Rates of resistant gram-positive and gram-negative bacteria also significantly declined. Age, the Acute Physiology and Chronic Health Evaluation score, solid organ transplantation, and malignancy were identified through logistic regression as risk factors for mortality. Antibiotic drug rotation was an independent predictor of survival. The incidence of VAP and catheter-related infections also declined during the rotation period.

Conclusion

Gram-negative nosocomial infection has become more common and more difficult to prevent and manage in this age of antimicrobial drug resistance. Understanding resistance mechanisms in common pathogens is essential to selecting appropriate empiric antimicrobial therapy. Inappropriate empiric therapy is associated with a significant excess mortality. Pharmacists must have an understanding of the strategies that have been effective in both combating resistance and improving antimicrobial prescribing.

Annotated Bibliography

1. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA* 2003;289:885–8.

The authors examined trends in national rates of antimicrobial resistance among gram-negative bacilli from patients in the intensive care unit (ICU) over the 10 years from 1990 to 2000, and compared these rates to antimicrobial use during this period. Using data collected from institutions in 43 states, antibiotic drug susceptibility results for 35,790 gram-negative bacilli between 1994 and 2000 were examined and compared to data from 1990 to 1993. The activity of most antimicrobial drugs against gram-negative isolates showed an absolute decrease of 6% or less over the study period. The overall susceptibility to ciprofloxacin decreased steadily from 86% in 1994 to 76% in 2000, and it was significantly associated with increased national fluoroquinolone use. Cross-resistance with gentamicin, ceftazidime, imipenem, and amikacin was observed for ciprofloxacin-resistant isolates of *Pseudomonas aeruginosa*, *Enterobacter* species, and *Klebsiella pneumoniae*. This study documented the increasing incidence of ciprofloxacin resistance among gram-

negative bacilli that has occurred coincident with increased fluoroquinolone use, and highlighted the antibiotic drug cross-resistance that can occur with ciprofloxacin-resistant isolates.

2. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462–74.

These investigators were among the first to evaluate the relationship between inadequate antimicrobial treatment of infections and hospital mortality for patients in the ICU. They screened 2000 consecutive patients admitted to the ICU, 655 of whom had either community-acquired or nosocomial infection. Inadequate antimicrobial therapy was defined as either no therapy or as a drug regimen that did not have in vitro activity against the causative pathogen. Among infected patients, 169 (25.8%) received inadequate antimicrobial treatment. The occurrence of inadequate antimicrobial treatment was most common among patients with nosocomial infections which developed after treatment of a community-acquired infection (45.2%), followed by patients with nosocomial infections alone (34.3%), and then patients with community-acquired infections alone (17.1%). Multiple logistic regression analysis using only the cohort of infected patients ($n = 655$), demonstrated that prior antibiotic drug administration, presence of a bloodstream infection, increasing Acute Physiology and Chronic Health Evaluation II scores, and decreasing patient age were independently associated with administering inadequate antimicrobial treatment. The hospital mortality rate of infected patients receiving inadequate antimicrobial treatment (52.1%) was statistically greater than the hospital mortality rate of the remaining patients in the cohort without this risk factor (12.2%). Similarly, the infection-related mortality rate for patients receiving inadequate antimicrobial treatment (42.0%) was significantly greater than the infection-related mortality rate of patients receiving adequate antimicrobial treatment (17.7%). Using a logistic regression model, inadequate antimicrobial treatment of infection was the most important independent determinant of hospital mortality for the entire patient cohort. The authors concluded that inadequate treatment of infections appears to be an important determinant of hospital mortality. Their data have subsequently been confirmed by other investigators.

3. Raymond DP, Pelletier SJ, Crabtree TD, et al. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit Care Med* 2001;29:1101–8.

This paper presented startling results of an antibiotic drug rotation program in a surgical ICU. Investigators developed an antibiotic drug rotation strategy for selecting empiric therapy to treat pneumonia, peritonitis, or sepsis of unknown origin. Data collected during the 1-year rotation program were compared to data collected during the previous year in which no rotation program was in place. No differences were noted in age, Acute Physiology and Chronic Health Evaluation II score, race, overall antibiotic drug use, or therapy duration between the 2 study years. Outcome analysis revealed significant reductions during the rotation in the incidence of antibiotic-resistant gram-positive cocci infections, antibiotic-resistant gram-negative bacillary infections, and mortality. Logistic regression identified age, Acute Physiology and Chronic Health Evaluation II score, solid organ transplantation, and malignancy as independent

predictors of mortality. Antibiotic drug rotation was an independent predictor of survival. The investigators found conclusively that quarterly rotation of empirical antibiotic therapy reduced infectious mortality in their ICU, and reduced both gram-positive and gram-negative bacterial resistance.

4. Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001;29:1109–15.

There are few clinical evaluations of any protocol to manage nosocomial infection. The authors have been instrumental in outlining the serious consequences of inappropriate antimicrobial therapy on outcome. A guideline for managing ventilator-associated pneumonia (VAP) was prospectively evaluated using a before-and-after study design. Between April 1999 and January 2000, 102 patients were prospectively evaluated, 50 in the period before the guidelines were implemented, and 52 in the period after implementation. The main outcome evaluated was the initial administration of adequate antimicrobial treatment as determined by respiratory tract cultures. Inadequate antimicrobial treatment was prospectively defined as administering an initial antimicrobial regimen without demonstrated *in vitro* activity against the identified bacterial species associated with VAP. Severity of illness using clinical pulmonary infection scores was similar for patients during the two treatment periods. Initial administration of adequate antimicrobial treatment was statistically greater during the period after guideline implementation compared with the period before implementation (94.2% vs. 48.0%; $p < 0.001$). The duration of antimicrobial treatment was statistically shorter with guideline use compared to the period before its implementation (8.6 ± 5.1 days vs. 14.8 ± 8.1 days; $p < 0.001$). A second episode of VAP occurred less often among patients after guideline implementation (7.7% vs. 24.0%; $p = 0.030$). Investigators demonstrated a straightforward approach to administering empiric appropriate antimicrobial therapy to patients with VAP using an institution-specific clinical guideline. The findings suggest that similar guidelines using local microbiological data can be used to improve overall antibiotic drug use for treating VAP and perhaps other nosocomial infections.

5. van Saene HK, Petros AJ, Ramsay G, Baxby D. All great truths are iconoclastic: selective decontamination of the digestive tract moves from heresy to level 1 truth. *Intensive Care Med* 2003;29:677–90.

Selective decontamination of the digestive tract has been studied for more than 2 decades, with few institutions using this technique to reduce the incidence of nosocomial infections. This review compared evidence of the effectiveness, costs, and safety of the traditional parenteral antibiotic-only approach against evidence gathered from 53 randomized trials involving more than 8500 patients and six meta-analyses on selective decontamination of the digestive tract to control infection in the ICU. The traditional approach to preventing nosocomial infection is handwashing aimed at preventing transmission of all microorganisms to control all infections that occur after 2 days in the ICU. The second feature is the restrictive use of systemic antibiotic drugs, for use only in cases of microbiologically proven infection. In contrast, selective decontamination of the digestive tract controls the three types of infection (primary,

secondary endogenous and exogenous) because of 15 potential pathogens. The classical selective decontamination of the digestive tract tetralogy comprises four components: a parenteral antibiotic drug, such as cefotaxime, administered for 3 days to prevent primary endogenous infections typically occurring “early”; the oropharyngeal and enteral antimicrobials, polymyxin E, tobramycin, and amphotericin B, administered in throat and gut throughout the treatment in the ICU to prevent secondary endogenous infections tending to develop “late”; a high standard of hygiene to control transmission of potential pathogens; and surveillance samples of the throat and rectum to monitor the efficacy of the treatment. This analysis focused on the end points of: infectious morbidity, mortality, antimicrobial resistance, and costs. The authors found that properly designed trials on handwashing have never demonstrated a reduction in either pneumonia and septicemia, or mortality. Two randomized trials using restrictive antibiotic drug policies failed to show a survival benefit at 28 days. In both trials, the proportion of resistant isolates obtained from the lower airways was greater than 60% despite significantly less use of antibiotic drugs in the test group. A formal cost-effectiveness analysis of the traditional antibiotic drug policies has not been performed. Two meta-analyses have shown selective decontamination of the digestive tract reduces the odds ratio for lower airway infections to 0.35 (0.29–0.41) and mortality to 0.80 (0.69–0.93), with a 6% overall mortality reduction from 30% to 24%. No increase in the rate of superinfections due to resistant bacteria could be demonstrated over 20 years of clinical research. Four randomized trials found the cost per survivor to be substantially lower in patients receiving selective decontamination of the digestive tract than for those traditionally managed. In this somewhat critical review, the authors conclude that traditionalists still rely on level 5 evidence (i.e., expert opinion) with a grade E recommendation, whereas the proponents of selective decontamination of the digestive tract cite level 1 evidence allowing a grade A recommendation in their attempts to control infection in the ICU. The main reason for selective decontamination of the digestive tract not being widely used is the primacy of opinion over evidence.

SELF-ASSESSMENT QUESTIONS

Questions 1–3 pertain to the following case.

T.F. is a 73-year-old woman who was admitted to the emergency department with a chief complaint of right lower extremity and right hip pain after a fall at home. Medical history includes type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, and osteoarthritis. She reports a severe allergy to penicillin. Current drugs at home are glipizide-metformin, lisinopril, metoprolol, furosemide, atorvastatin, albuterol-ipratropium inhaler, celecoxib, sublingual nitroglycerin, and acetaminophen. She smokes about one-half pack of cigarettes per day, and denies any alcohol use. Subsequent evaluation confirms a right hip fracture, and T.F. goes for open reduction and internal fixation the following morning. She received one preoperative dose of cefazolin 1 g intravenously, and continues to receive cefazolin 1 g intravenously every 8 hours for 48 hours postoperatively. After surgery, T.F. is unable to be weaned from mechanical ventilation and is transferred to the surgical intensive care unit (ICU). During her first 72 hours in the ICU, her respiratory status (gas exchange) deteriorates, urine output decreases, serum creatinine increases from a baseline of 1.3 mg/dl to 3.8 mg/dl, her white blood cell count increases to 18,900 cells/mm³, she is spiking fevers, and is pan-cultured. Respiratory secretions are copious, thick, and brown. Initial microbiology results reveal the following: paired blood cultures both negative; urine culture (and urinalysis) negative; and sputum culture has heavy growth of *Enterobacter aerogenes*.

1. Which one of the following is an independent risk factor for T.F. developing a nosocomial infection?
 - A. Use of an inhaler.
 - B. Hip fracture.
 - C. Prior administration of antibiotic drugs.
 - D. History of smoking.
2. Which one of the following is the most likely type of resistance you would expect to encounter in T.F.'s nosocomial infection (*E. aerogenes* pneumonia)?
 - A. Extended-spectrum β -lactamase (ESBL)/AmpC β -lactamase production.
 - B. Porin channel deletion.
 - C. Efflux pump expression.
 - D. Resistance is not a problem with *E. aerogenes* infections.
3. Given the limited microbiological data in this case, which one of the following is the best antibiotic drug regimen for T.F.'s nosocomial infection?
 - A. Imipenem-cilastatin.
 - B. Ceftazidime.
 - C. Ceftriaxone.
 - D. Azithromycin.
4. The pharmacy and therapeutics committee at your institution has created a task force to evaluate scheduled antibiotic drug rotation in the medical/surgical ICU. The project goals are to improve the selection of appropriate empiric therapy for nosocomial infections and reduce the overall gram-negative bacterial antibiotic drug resistance. The task force has recommended a cycling regimen for pneumonia and intra-abdominal infections. Which one of the following strategies would be best in designing the cycling scheme?
 - A. Cycle levofloxacin alternatively with ciprofloxacin.
 - B. Cycle combination regimens with monotherapy regimens.
 - C. Rest one antibiotic drugs class during each cycle.
 - D. Cycle the use of an antibiotic drug class between pneumonia and intra-abdominal infections.

5. A 57-year-old man sustained several rib fractures, a broken clavicle, and severe lung contusions in a motor vehicle accident; as a result, he has had a long and complicated ICU course. He developed bacteremia with multidrug-resistant *Pseudomonas aeruginosa* isolated from two consecutive blood cultures. The susceptibility testing showed the organism to be resistant to all antibiotic drugs tested. The patient developed septic shock and worsening renal function (serum creatinine 2.9 mg/dl) with severe metabolic acidosis, and the intensivist ordered colistin (9,000,000 IU/day intravenously [2.5 mg/kg] divided into three dosages). In managing this patient's infection, which one of the following is the best action to take?
- Recommend a dose change to 5 mg/kg/day.
 - Recommend increasing fluid intake to produce a brisk diuresis.
 - Continue colistin therapy for a full 21 days.
 - Recommend combination therapy with colistin and amikacin.
6. Differentiating ESBL-mediated resistance from AmpC-mediated resistance is important for which one of the following reasons?
- Ceftazidime use is ineffective for AmpC β -lactamase resistance but not ESBL resistance.
 - AmpC β -lactamase is not inhibited by tazobactam or clavulanic acid.
 - Piperacillin-tazobactam would be indicated for the isolate producing an AmpC β -lactamase.
 - Cefepime is indicated for organisms expressing ESBL-mediated resistance.

Questions 7 and 8 pertain to the following case.

A patient with nosocomial bacteremic pneumonia has a *P. aeruginosa* isolate cultured from his bloodstream. The isolate has the following susceptibility profile.

Aztreonam	R
Amikacin	S
Ceftazidime	R
Cefepime	S
Ciprofloxacin	R
Gentamicin	S
Imipenem	S
Meropenem	R
Piperacillin	R
Ticarcillin	S
Tobramycin	S

R = resistant; S = susceptible.

7. The resistance mechanism most likely present in this organism is which one of the following?
- AmpC β -lactamase.
 - MexX-MexY-OprM efflux system.
 - Plasmid-mediated carbapenemase.
 - MexA-MexB-OprM efflux system.
8. Which one of the following drug therapies should be chosen to treat this patient's infection?
- Cefepime 2 g intravenously every 8 hours.
 - Imipenem 500 mg intravenously every 6 hours.
 - Cefepime 2 g intravenously every 8 hours plus tobramycin 7 mg/kg intravenously every 24 hours.
 - Piperacillin-tazobactam 3.375 g intravenously every 6 hours plus gentamicin 7 mg/kg intravenously every 24 hours.
9. An institution with a high rate of imipenem-resistant *P. aeruginosa* is considering a formulary change to meropenem. Which one of the following statements best describes this decision?
- If the institution also has a high rate of *P. aeruginosa* overexpression of efflux systems, such as the MexA-MexB-OprM, the change to meropenem is not warranted.
 - If the institution also has a high rate of *P. aeruginosa* overexpression of efflux systems, such as the MexA-MexB-OprM, the change to meropenem should be beneficial.
 - Regardless of the mechanisms of imipenem resistance, meropenem minimum inhibitory concentrations (MICs) against *P. aeruginosa* remain well below the Clinical and Laboratory Standards Institute breakpoint.
 - Regardless of the mechanisms of imipenem resistance, meropenem MICs against *P. aeruginosa* parallel those of imipenem.
10. A hospital has reported rising *P. aeruginosa* resistance to ceftazidime over the past 4 years. Which one of the following strategies would be effective to mitigate this resistance pattern?
- Make a substitution of cefepime whenever ceftazidime is ordered.
 - Restrict ceftazidime use in the hospital until resistance rates decline.
 - Reduce carbapenem use through restriction to the infectious disease service.
 - Rotate antibiotic drugs in the hospital, with a period in which no fluoroquinolones are used.
11. There has been an outbreak of multidrug-resistant *Acinetobacter baumannii* in an ICU for the past 4 months. Which one of the following is the most useful intervention?
- Acinetobacter* outbreaks are self-limiting; no intervention is necessary to reduce colonization.
 - Patients in the ICU should routinely receive aerosolized ampicillin-sulbactam to decrease the level of upper airway colonization.
 - All patients should receive imipenem empirically when nosocomial infection is suspected.
 - All patients should receive ceftazidime empirically when nosocomial infection is suspected.
12. Inadequate empiric antimicrobial therapy has been strongly associated with increased mortality in acutely ill patients in ICUs. Which one of the following strategies has been effective in improving the prescribing of appropriate empiric therapy?
- Antimicrobial rotation.
 - Selective decontamination of the digestive tract.
 - Pharmacodynamic dose individualization.
 - Antibiotic drug restriction.

13. The infectious diseases service in an institution has suggested empiric combination antimicrobial therapy for all suspected cases of nosocomial pneumonia. Which one of the following is an appropriate response from the department of pharmacy to this proposal?
- Because there are not sufficient data in the literature to support combination therapy, all patients should receive empiric monotherapy.
 - All patients should receive vancomycin as a component of their empiric therapy.
 - Patients with nosocomial infections suspected to be caused by nonfermentative gram-negative bacilli may respond better to combination therapy.
 - Early-onset ventilator-associated pneumonia (VAP) should receive combination therapy against *Streptococcus pneumoniae* and atypical bacteria.
14. Selective decontamination of the digestive tract appears to reduce the risk of lower airway infections and positively affects survival with no increase in the superinfection rate due to resistant bacteria. Which one of the following concerns may impede selective decontamination of the digestive tract use in an ICU?
- Large number of mechanically ventilated patients.
 - Low rate of nosocomial infections in the unit.
 - Invasive nature of the intervention.
 - Potential impact on resistance and cost.
15. Which one of the following is a relatively common change in antimicrobial pharmacokinetics in critically ill patients compared to noncritically ill patients?
- Increased volume of distribution.
 - Increased absorption of oral and transdermal drugs.
 - Decreased clearance because of hypermetabolic state.
 - Increased protein binding.
16. Which one of the following empiric dosing adjustments should be considered in critically ill patients compared to data from healthy volunteers?
- Decrease the dose.
 - Increase the dose.
 - Increase dosing interval.
 - Monitor free (unbound) serum concentrations.
17. Which one of the following is associated with improved outcomes when using fluoroquinolones in gram-negative infections?
- Peak-MIC ratio less than 10.
 - Percent of time that serum concentration exceeds MIC at least 60%.
 - Area under the concentration-time curve-MIC value 125–250.
 - Doses greater than 10–15 mg/kg/day.
18. Which one of the following conclusions is supported by available evidence on the duration of antimicrobial therapy for VAP?
- Changes in therapy should only be made 5–7 days after initiating therapy, allowing time for full assessment of patient response.
 - No published data are available to support discontinuing antimicrobial therapy for VAP before 10–14 days.
 - Treatment duration less than the traditional 10–14 days is associated with increasing rates of resistance and mortality.
 - Studies comparing shorter therapy courses to standard, longer courses have demonstrated similar morbidity and mortality.
- Questions 19–21 pertain to the following case.**
- J.F. is a 68-year-old man admitted to the surgical ICU after a partial esophagectomy (distal one-third) for resection of an esophageal adenocarcinoma. J.F.'s medical history includes hypertension, hypercholesterolemia, and atrial fibrillation. He denies any allergies. J.F. is stable during the first 48 hours, but on postoperative day 2, he becomes tachycardic (heart rate is 110–120 beats/minute) and hypotensive (systolic blood pressure 70–80 mm Hg). He is febrile (102.7°F) and his white blood cell count is 22,800 cells/mm³. He is aggressively fluid resuscitated and low-dose vasopressors are initiated. He is endotracheally intubated for impending respiratory failure and is placed on mechanical ventilation. He has a nasogastric tube and a Foley catheter in place. Blood, sputum, and urine cultures are obtained. A computed tomography scan reveals fluid in the mediastinal space suspicious of an anastomotic leak. J.F. is 5'11", and weighs 78 kg. His urine output has remained stable at about 50–100 ml/hour, and his current serum creatinine is 1.3 mg/dl.
19. Which one of the following is the best statement regarding empiric therapy for J.F.?
- The most effective approach to antimicrobial therapy would be to await preliminary culture results to guide definitive therapy.
 - Empiric therapy should be narrow, and geared toward pathogens likely to be encountered from a mediastinal source.
 - Empiric therapy should be broad-spectrum and initiated as soon as possible.
 - If *P. aeruginosa* is suspected, monotherapy with an antipseudomonal β -lactam should be started until susceptibility data and synergy testing are done.
20. Which one of the following is best supported by evidence regarding empiric therapy for J.F.'s nosocomial infection?
- Ceftazidime 1 g intravenously every 8 hours.
 - Cefepime 2 g intravenously every 8–12 hours.
 - Levofloxacin 500 mg intravenously every 24 hours.
 - Piperacillin 3 g intravenously every 6 hours.

Initial reports show that all three blood cultures are positive for nonfermentative gram-negative bacilli. J.F.'s clinical condition has not changed in the past 48 hours. He remains febrile and still has a leukocytosis.

21. Which one of the following is the best course of action based on these data?
- A. Increase the dose and/or change the dosing interval of the currently prescribed antimicrobial regimen to maximize its pharmacodynamic effects.
 - B. Discontinue the current antibiotic drug and start imipenem-cilastatin 500 mg intravenously every 6 hours.
 - C. Discontinue the current antibiotic drug and start imipenem-cilastatin 500 mg intravenously every 6 hours plus tobramycin 7 mg/kg/day intravenously every 24 hours.
 - D. Discontinue antibiotic drugs until final culture and susceptibility reports available.
22. Which one of the following is part of the rationale behind administering β -lactam therapy by continuous infusion?
- A. β -Lactams exhibit concentration-independent killing.
 - B. β -Lactams have a significant postantibiotic drug effect.
 - C. The desire to achieve a MIC of more than 125.
 - D. β -Lactams have a relatively long elimination half-life.
23. Which one of the following best describes the recent epidemiology trends regarding bloodstream infections in the ICU?
- A. Most nosocomial bloodstream infections are caused by gram-negative organisms.
 - B. Gram-negative organisms have not been common pathogens since the introduction of broad-spectrum antibiotic drugs, such as the fluoroquinolones and third- and fourth-generation cephalosporins.
 - C. Although most central venous catheter-related bloodstream infections are caused by gram-positive bacteria, bacteremia secondary to VAP, urinary tract infections, and intra-abdominal infections often are caused by gram-negative bacteria.
 - D. Nosocomial gram-negative bloodstream infections are easily and successfully treated by intravenous antimicrobial drugs achieving excellent serum concentrations.
24. Which one of the following strategies has been effective in decreasing resistance rates within an institution or part of an institution?
- A. Antimicrobial rotation.
 - B. Clinical guidelines for VAP.
 - C. Pharmacokinetic consult programs.
 - D. Synergistic combination therapy.
25. Which one of the following is part of the rationale behind using extended-interval aminoglycoside dosing?
- A. Aminoglycosides exhibit concentration-independent killing.
 - B. The desire to achieve a peak-MIC ratio of at least 10.
 - C. The desire to achieve time of the serum concentration above the MIC of at least 60–70%.
 - D. Aminoglycosides have a relatively long elimination half-life.