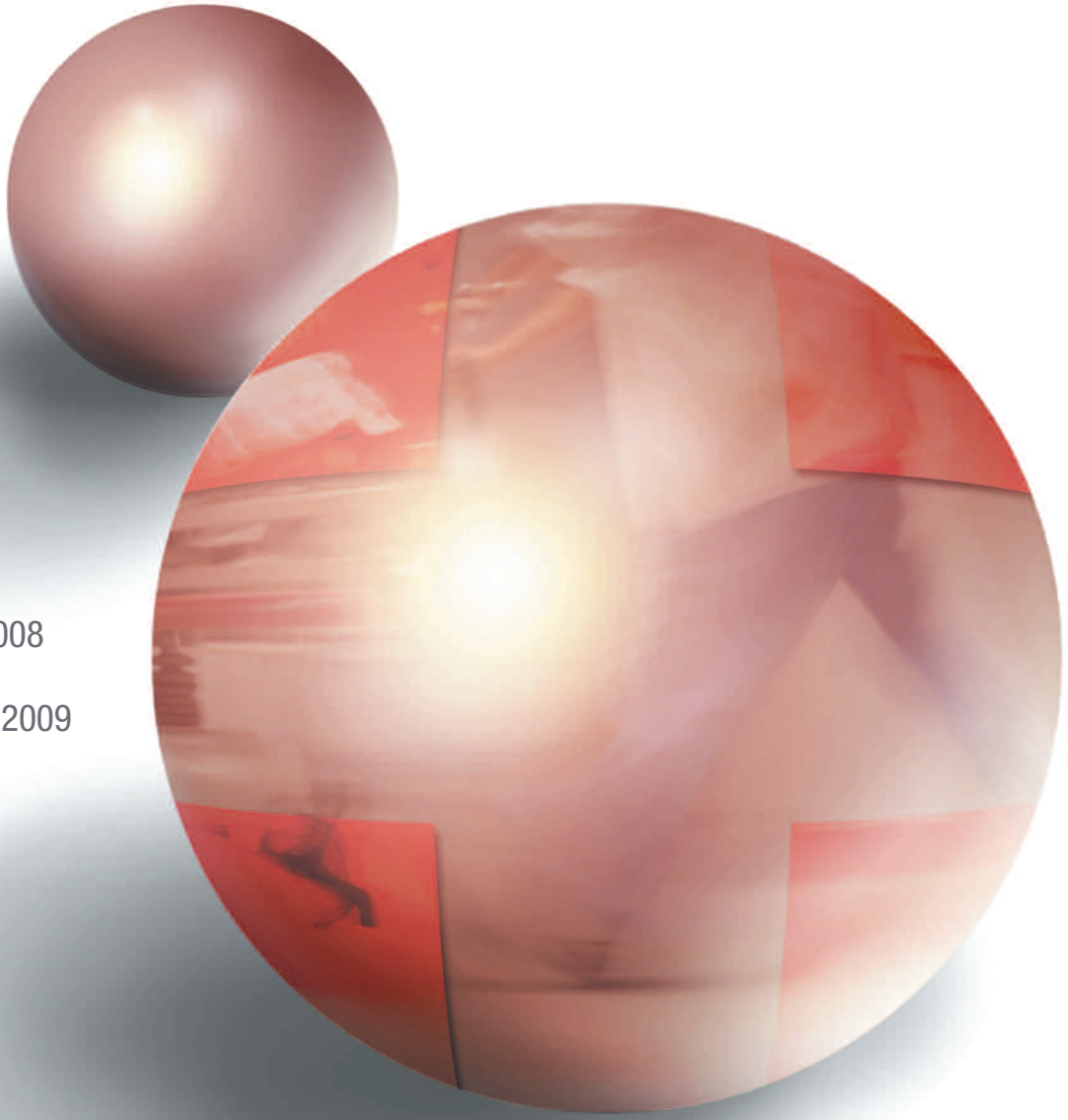
Antibiotics: Practice Pearls for the Emergency Department Physician



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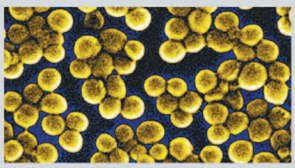
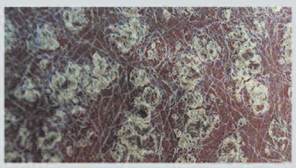
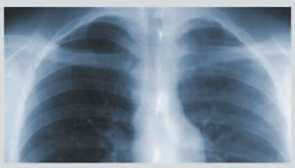

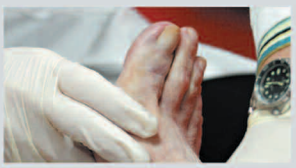

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Antibiotics: Practice Pearls for the Emergency Department Physicians has been developed to provide an overview of the general principles of antibiotic therapy and includes a review the current classes of antibiotics available to the emergency department (ED) physician and outlines their place in the clinical armamentarium. Aspects such as indications, dosing schedules, and common adverse effects will be discussed.

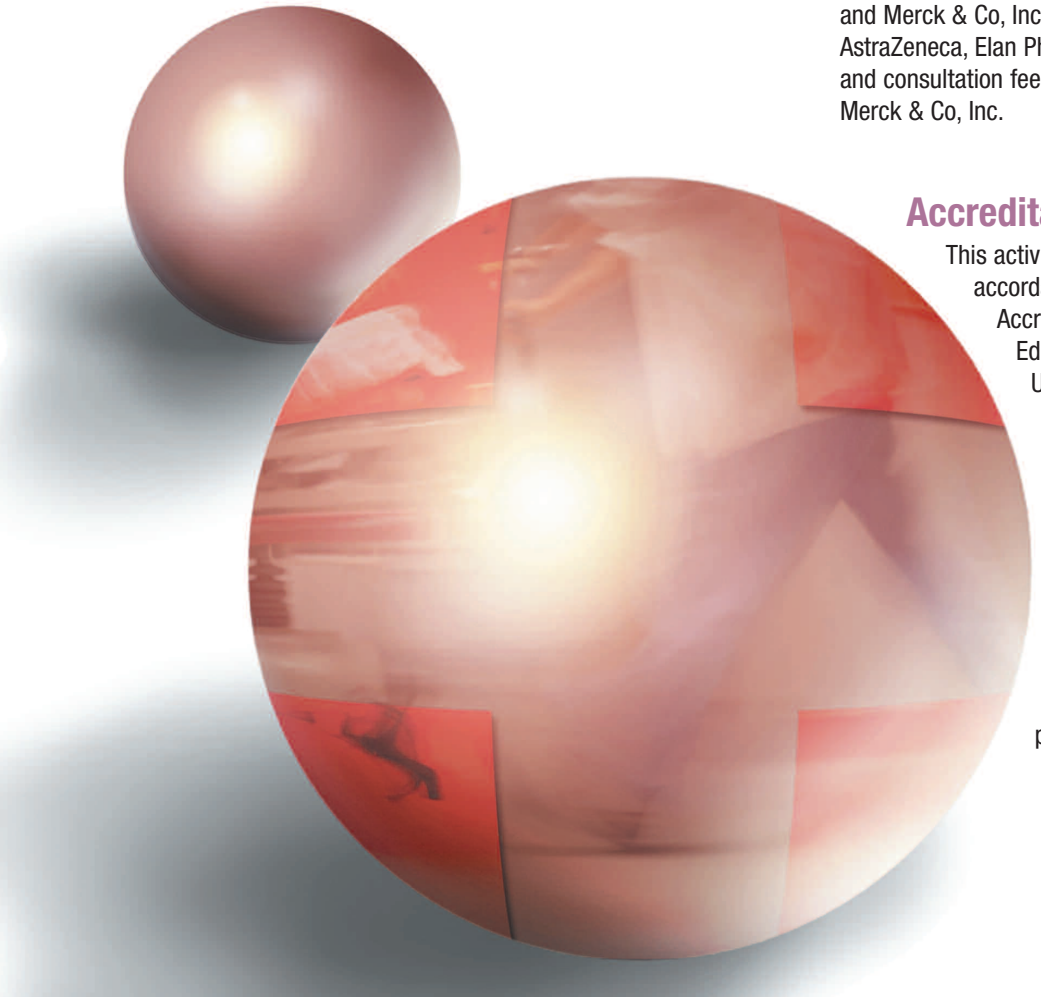
Target Audience

This activity has been developed for emergency medicine physicians and other healthcare professionals involved in the diagnosis and treatment of patients with infectious diseases (ID) presenting to the emergency department.

Learning Objectives

Upon completion of this activity, participations should be better able to:

- Recognize the key issues of managing patients with common ID disorders presenting in the ED and treat patients appropriately against a background of increasing antibiotic resistance
- List key principles of antibiotic therapy, including the importance of early, broad-spectrum antibiotics in high-risk patients
- Outline currently available and emerging antibiotics and discuss the criteria for appropriate antibiotic selection in the ED



Method of Participation

This newsletter should take approximately 1 hour to complete. The participant should, in order, review the learning objectives, review the activity, and complete and submit the CME Registration/Posttest/Evaluation form to the University of Kentucky College of Medicine to receive credit. Participants will have the opportunity to comment on the extent to which the learning objectives were met, the quality of the instructional process and the perception of commercial bias and participant views on future educational needs.

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Faculty Disclosure

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Dr. Paterson has received honoraria for his role in a speakers bureau for AstraZeneca, Cubist Pharmaceuticals, Elan Pharmaceuticals, Inc, and Merck & Co, Inc. He has received research grants from AstraZeneca, Elan Pharmaceuticals, Inc, Merck & Co, and Pfizer, Inc and consultation fees from Acureon Pharma, Johnson & Johnson, and Merck & Co, Inc.

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General Principles of Antibiotic Therapy

The ED physician is called upon to diagnose and initiate empiric therapy of a broad spectrum of infectious diseases. As such, they must have a broad knowledge of the principles of antibiotic therapy and in-depth knowledge about the properties of the various classes of antimicrobial drugs and their individual members. In general, antibiotic therapy can be broadly classified into 3 types: empiric, definitive, and prophylactic. In the practice of emergency medicine, empiric therapy is often required. There are a number of host and drug factors that must be considered in initiating antibiotic therapy.

Host/Microbial Factors

SEVERITY OF THE INFECTION

The severity of the infection can be gauged by a number of factors. The American College of Chest Physicians (ACCP), in conjunction with the Society of Critical Care Medicine (SCCM), established definitions for infection, the systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis in the early 1990s. These definitions have stood the test of time (Table 1).[1] The classification of sepsis uses presence of the ≥2 SIRS criteria *plus* the presence of documented or suspected infection. The necessity of infection should be obvious from the lack of specificity of the SIRS criteria. As one observer noted, "since he's out of shape and gets tachycardia and tachypnea with exercise, he meets 2 SIRS criteria every time he climbs a flight of stairs." Sepsis then is the presence of ≥2 SIRS criteria in an infected patient. As such, many patients that are seen in the ED are septic. Severe sepsis is documented or suspected infection in a patient with ≥2 SIRS criteria with acute organ dysfunction. Septic shock and the multiple organ dysfunction syndrome then are subsets of severe sepsis. Although the mortality for patients meeting the ACCP/SCCM criteria for infection and sepsis does not differ, it increases progressively from sepsis to severe sepsis to septic shock. In patients with severe sepsis, the mortality increases with the number of acute organ dysfunctions. Clearly, patients with severe sepsis are seriously ill and require hospitalization.

The patients with potentially life-threatening infections should receive immediate empiric therapy with ≥1 drugs that have activity against the pathogens believed to be responsible. The drugs should be administered intravenously within the first hour of the diagnosis after appropriate cultures have been taken.[2] Should the presentation subsequently be determined to be non-infectious, antimicrobial therapy should be stopped immediately to prevent the development of resistance.

Table 1. ACCP/SCCM Criteria for SIRS, Sepsis, Severe Sepsis, Septic Shock, and Multiple Organ Dysfunction Syndrome

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

The systemic inflammatory response to a wide variety of severe clinical insults, manifestedd by two or more of the following conditions:

1. Temperature >38ºC or <36ºC
2. Heart rate >90 beats/minute
3. Respiratory rate >20 breaths/minute or $PaCO_2$ <32 mm Hg
4. White blood cell count >12,000/µL or <4000/µL, or 10% immature (band) forms

SEPSIS – The systemic inflammatory repsonse to a documented infection. In association with infection, manifestations of sepsis are the same as those prevviously defined for SIRS. It should be determined whether they are a direct systemic response to the presence of an infectious process and represent an acute alteration from baseline in the absence of other known causes for such abnormalities. The clinical manifestations would include two or more of the SIRS criteria (above) as a result of documented infection.

SEVERE SEPSIS/SIRS – Sepsis (SIRS) associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

SEPSIS (SIRS)-INDUCED HYPOTENSION – A systolic blood pressure <90 mm Hg or a reduction of ≥40 mm HG from baseline in the absence of other causes for hypotension.

SEPTIC SHOCK/SIRS SHOCK – A subset of severe sepsis (SIRS) and defined as sepsis (SIRS) induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic (SIRS) shock.

MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS) – Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Reprinted with permission from *Chest*.[1]

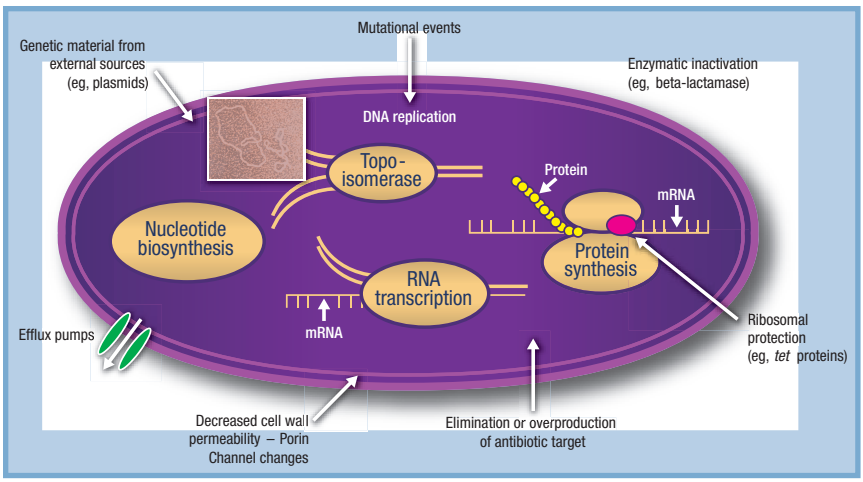
HOST FACTORS

The ability of the host to respond to the infection is a critical element in the selection of antibiotic agents. All limbs of the immune (innate, humoral, cellular) system play a role. If a patient is neutropenic, the bacteriostatic properties of a drug are not likely to be beneficial. Impaired opsonic activity places patients with defects of humoral immunity and components of complement at increased risk from infections due to encapsulated organisms. AIDS is an example of a disease in which impaired cellular immune capacity places them at risk for a variety of viral, fungal, parasitic, and bacterial infections.

The site of infection is another important host factor. For example, a drug's antibacterial properties may be significantly decreased in an abscess cavity. This is because of a number of factors including increased impaired blood supply due to increased hydrostatic pressure within the abscess and the presence of cellular debris and proteins in the pus that may inactivate the drug. Every patient presenting with a serious infection should be evaluated for a focus of infection that can be addressed by source control. Source control measures include removal of a foreign body, drainage of an abscess, debridement of necrotic tissue, closing of a gastrointestinal perforation. In some instances, source control will be enough to allow the host defenses to eliminate the infection. For example, a recent analysis by Hankin and Everett and other recent reports have concluded that patients with an abscess who are treated with incision and drainage (I&D) recover at the same rate as those who get an I&D plus antibiotics.[3]

Other factors that must be considered include history of allergies, age, pregnancy, and comorbidities. Patients often give a history that a specific antibiotic produced a drug reaction—some are real, some are not. A specific history of an anaphylactic reaction precludes the use of an antibiotic except in the most extreme circumstances. Desensitization procedures may be tried when there are no alternate antibiotics in a patient with a life-threatening infection. Both tetracyclines and fluoroquinolones accumulate in the developing skeleton.

Figure 1. Methods of Bacterial Resistance to Antibiotic Drugs.



Adapted with permission from Chopra I.[5]

Consequences of tetracycline administration to children include staining of teeth and dental or skeletal hypoplasia. Fluoroquinolones can produce reversible joint symptoms in children and tendinitis and tendon rupture in adults. Treatment during pregnancy is associated with the potential for toxicity in both the mother and the fetus. In addition, the pharmacokinetic properties of various drugs are altered during the gestation. Renal function declines with advancing age; therefore, the elderly may not clear drugs to the same extent as a young person. This can lead to toxicity at a drug level that would not affect a younger person.

INFECTING ORGANISM

The infecting organism and the likelihood that specific infections are in and of themselves potentially life threatening are important considerations in therapy. Patients with meningococcemia, for example, may progress from sepsis to fulminant meningococcemia and death within hours. On the other hand, many patients with community-acquired pneumonia (CAP) can be treated with oral antibiotic and sent home. Another microbial factor that is producing a significant shift in practice is the likelihood that a patient is infected with a drug-resistant organism.[4] Drug-resistant organisms are increasingly important causes of infection in patients from the community. Their increasing prevalence is due to a number of factors including indiscriminate use of antibiotics and dissemination of organisms from the healthcare environment into the community. The increasing importance of drug-resisant organisms in the community is emphasized by the recent description of healthcare-acquired pneumonia (HCAP): a distinct form of pneumonia presenting from the community with clinical and microbiologic features that more closely resemble hospital-acquired pneumonia (HAP) than CAP.

Drug Factors

PHARMACOKINETIC ISSUES

Successful antibiotic therapy requires that the drug reach the site of infection and be present in concentrations high enough to inhibit or kill the bacteria without harming the host. Oral administration is often the preferred route. However, patients with serious infections may need parenteral antibiotics to ensure that predictable concentrations of the drug are attained in the infected site. Drug levels should at least reach the minimum inhibitor concentration (MIC) for the organism and, preferably, should be several orders of magnitude higher. In most instances, antibiotics penetrate into the infected focus by passive diffusion. Therefore, drugs that are protein bound may not penetrate the infected site as well as those with less protein binding.

Another important factor is whether the drug's bacteriocidal properties are concentration or time dependent. For example, the bacteriocidal properties of the beta-lactams are primarily time dependent while aminoglycosides kill by a concentration-dependent mechanism. It is also important to know the status of the patient's renal and hepatic function. Most drugs are excreted by the kidneys; therefore, impaired renal function may require an alteration in the dosing regimen (eg, aminoglycosides are eliminated entirely by the kidneys).

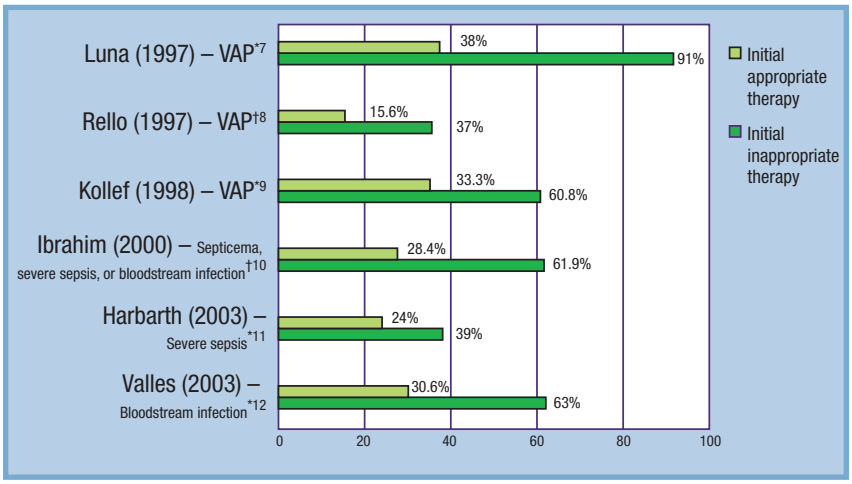
BROAD- OR NARROW-SPECTRUM DRUGS?

Initial empiric therapy should include ≥1 drugs that are active against the likely infecting organism and will penetrate into the infected site. Susceptibility should be determined from an antibiogram that indicates the resistance pattern of the species in the community or institution. The antibiograms should be updated on at least an annual basis, easily accessible by the medical staff, report temporal trends in susceptibility, and report susceptibility results separately for different anatomic sites (eg, blood, urine, wounds).

There is abundant evidence that failure to initiate the appropriate antibiotic as early as possible adversely influences outcomes (Figure 2).[6-12] Although this association has been most conclusively demonstrated in patients who are critically ill with septicemia, severe sepsis, or community-acquired bloodstream infection, it is reasonable to believe that it is also valid for less serious infections.

The empiric antibiotic regimen should be sufficiently broad to cover all likely pathogens. In patients who are severely ill, combination therapy may be appropriate. To limit superinfection and prevent the emergence of resistant organisms, broad-spectrum antibiotics should not be used indiscriminately. However, patients with severe sepsis or septic shock should receive broad-spectrum drugs until the responsible organism has been identified and its susceptibility determined. At that time, antibiotic therapy can be deescalated to narrower-spectrum agents.

Figure 2. Mortality Associated With Initial Inappropriate‡ Therapy[6-12]



*Crude (overall mortality)
†Infection-related mortality
‡Based on the 2005 ATS/IDSA guidelines for the HAPV/VAP/HCAP,[6] inappropriate would be the term used to refer to the inadequate therapy noted in this figure.

Beta-Lactam Antibiotics

PENICILLINS

Although penicillin itself is now most commonly used for treatment of confirmed meningococcal or streptococcal infections and syphilis, the penicillins as a broader group remain important components of the antibiotic armamentarium (Table 2). For example, antibiotics such as piperacillin/tazobactam or amoxicillin/clavulanate are commonly used penicillins in ED practice.

Practice Pearl

As the name implies, MRSA is a drug resistant (in fact, multidrug-resistant) strain of S aureus. Community-acquired MRSA is now the most common identifiable cause of acute, purulent skin and soft tissue infections in United States Emergency Departments.

The penicillins can be divided functionally into the following:

- Antienterococcal penicillins, eg, ampicillin, amoxicillin
- Antienterococcal penicillins plus beta-lactamase inhibitors, eg, ampicillin/sulbactam, amoxicillin/clavulanate
- Antistaphylococcal penicillins, eg, nafcillin, dicloxacillin
- Antipseudomonal penicillins, eg, piperacillin, ticarcillin
- Antipseudomonal penicillins plus beta-lactamase inhibitors, eg, piperacillin/tazobactam, ticarcillin/clavulanate

As a general mode of action, the penicillins bind to penicillin-binding proteins (PBPs) and inhibit cell wall synthesis. There are 2 major mechanisms of resistance of bacteria to the penicillins. The first is alteration of the PBPs so that they have low affinity for the penicillins. As a result, cell wall synthesis is not affected and bacterial killing does not result. Important organisms which display this means of resistance are *Streptococcus pneumoniae* and *S aureus*. Methicillin resistant *S aureus* (MRSA) is caused by a gene *(mecA)* that encodes a mutated PBP called PBP2a. No penicillins have activity against MRSA.

The second major mechanism of bacterial resistance to penicillins is the production of beta-lactamases. These enzymes destroy beta-lactam antibiotics, including the penicillins. This process renders the bacteria resistant to the antibiotic destroyed. There are a huge variety of beta-lactamases, each of which has different abilities to destroy various penicillins. For example, the beta-lactamase frequently produced by *S aureus* destroys penicillin but not nafcillin.

Addition of a beta-lactamase inhibitor to a penicillin expands the coverage of the penicillin so it is free to kill beta-lactamase–producing organisms. In particular, it enhances the coverage of the organism against methicillin-susceptible *S aureus* (MSSA), some beta-lactamase–producing gram-negative bacilli and beta-lactamase–producing anaerobes such as *Bacteroides fragilis*. Therefore, it is unnecessary to add nafcillin to an antibiotic such as piperacillin/tazobactam because the beta-lactamase inhibitor inactivates the beta-lactamase produced by *S aureus*, allowing piperacillin unfettered antistaphylococcal activity. It is important to remember, however, that addition of a beta-lactamase inhibitor to a penicillin does not give the antibiotic activity against MRSA, because the underlying mechanism of resistance mediated by MRSA is a mutated PBP, not beta-lactamase production.

Practice Pearl

It is unnecessary to add metronidazole to antibiotic combinations such piperacillin/tazobactam, ampicillin/sulbactam, or amoxicillin/clavulanate because these antibiotics have extremely powerful antianaerobic activity, including against B fragilis.

Table 2. The Role of Common Penicillins in ED Practice

	MRSA	MSSA	Streptococci	Enterococci* (eg, *Escherichia coli, Klebsiella*)	"Gut bugs"	*Pseudomonas aeruginosa*	Anaerobes (eg, *Bacteroides fragilis*)
Penicillin	-	-	+++†	++	-	-	-
Amoxicillin	-	-	+++	+++†	+	-	-
Amoxicillin/clavulanate	-	+++	+++	+++	++	-	+++
Ampicillin	-	-	+++	+++	+	-	-
Ampicillin/sulbactam	-	+++	+++	+++	++	-	+++
Nafcillin	-	+++†	++	-	-	-	-
Piperacillin	-	-	++	++	+	++	-
Piperacillin/tazobactam	-	+++	++	++	++	++	+++

Legend: - no activity; + a reliable choice only if confirmed as susceptible by the laboratory; ++ a perfectly reasonable choice in most situations, +++ typically excellent activity against this organism *Not vancomycin-resistant enterococci
†The drug of choice for this organism
MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S aureus*

Most penicillins are available in an intravenous (IV) formulation, with a few exceptions (eg, amoxicillin/clavulanate). All penicillins have time-dependent killing characteristics, which means that their activity is optimized by having an elevated antibiotic concentration for a prolonged period of time between doses. Therefore, it is typical for penicillins to be given ≥3 times per day (and sometimes as much as 6 times per day).

Allergic reactions to penicillins are reasonably common but are known to be over-reported. Despite this, it is important to remember that a history of allergic reactions to 1 penicillin means that no other penicillin should be used in this patient.

Practice Pearl

It is essential to ask the patient the nature of reported penicillin allergy. If patients have a history of anaphylaxis, lip or throat swelling, or an urticarial rash, do not use a cephalosporin. If other reactions have occurred, it is generally safe to use a cephalosporin.

CEPHALOSPORINS

Cephalosporins are a widely used antibiotic class with a long track record of excellent safety/tolerability. Many clinicians are confused by the characteristics of the different generations of cephalosporins. In general, there is a change in spectrum of each generation of cephalosporin. This is summarized in Table 3 below.

The key clinical utility of the currently available cephalosporins is directly linked to the in vitro activity and can be summarized as follows:

Cefazolin	Perioperative surgical wound infection prophylaxis
Cephalexin	Oral antistaphylococcal (not MRSA)
Cefuroxime	Oral therapy for respiratory infections or urinary tract infections (UTIs)
Cefoxitin	Perioperative surgical wound infection prophylaxis (colorectal surgery)
Ceftriaxone	CAP; empiric therapy for suspected bacterial meningitis
Ceftazidime	Empiric therapy for *Pseudomonas* infections
Cefepime	Empiric therapy for *Pseudomonas* infections

The cephalosporins are rapid killers of most pathogens. Their dosing depends on their half-life and also the particular infection being targeted. For example, ceftriaxone is dosed at 1 g q24h for CAP yet is dosed at 2 g q12h for suspected bacterial meningitis. Reflecting their time-dependent killing activity, some authors have evaluated cefepime or ceftazidime via administration as a continuous infusion.

Ceftobiprole is a new broad-spectrum cephalosporin that has been granted "fast-track" status from the FDA. Phase III data indicate that, unlike the other cephalosporins, the drug has broad-spectrum activity against MRSA. Initial indications are sought for complicated skin and skin structure infections (eg, diabetic foot infections). In the trials, ceftobiprole was well tolerated. The most common treatment-associated adverse events were nausea, altered taste, vomiting, and diarrhea.

Cephalosporins are typically avoided in patients with a history of anaphylaxis, angioedema, or urticaria after exposure to penicillins. Rarely, patients may develop a rash with cephalosporins even though they had

Table 3. Cephalosporin Use by Generation

Generation	MRSA	MSSA	*S pneumoniae*	*Enterobacteriaceae*	*Pseudomonas*
1st (eg, cefazolin, cephalexin)	-	+++	+	+	-
2nd (eg, cefuroxime)	-	++	++	++	-
2nd (cephamycins, eg, cefoxitin)	-	+	+	++	-
3rd (eg, ceftriaxone)	-	+++	+++	++	-
3rd (eg, ceftazidime)	-	-	-	++	+++
4th (eg, cefepime)	-	+++	+++	+++	+++
5th (eg, ceftobiprole)	+++	+++	+++	++	+++

no adverse reactions to penicillins. Several studies have identified cephalosporin administration as a risk factor for *Clostridium difficile*–associated diarrhea.

AZTREONAM

Aztreonam has activity against aerobic gram-negative bacilli, including *P aeruginosa*. However, the in vitro activity of the drug is declining because of the advent of beta-lactamases and other mechanisms of resistance. The major place for aztreonam is to treat gram-negative infections in patients with adverse reactions to other beta-lactam antibiotics, and in whom aminoglycoside or quinolone usage is not appropriate.

CARBAPENEMS

Practice Pearl

Ertapenem differs from other available carbapenems in that it lacks significant activity against Acinetobacter spp. and P aeruginosa.

The currently available carbapenems are meropenem, imipenem, and ertapenem. A fourth carbapenem, doripenem, is in advanced stages of clinical development. The carbapenems are renowned for their activity against multidrug-resistant gram-negative bacilli. This is because they are not destroyed by most of the beta-lactamases produced by gram-negative organisms. Carbapenems are regarded as the drugs of choice for extended-spectrum beta-lactamase (ESBL)–producing organisms, such as *Klebsiella pneumoniae* or other *Enterobacteriaceae*. Meropenem, imipenem, and doripenem have activity against most strains of *P aeruginosa* or *Acinetobacter baumannii*, although resistance is increasing. A practical issue is the development of resistance of *P aeruginosa* to meropenem or imipenem occurring during therapy. Ertapenem lacks clinically useful activity against *P aeruginosa* or *A baumannii*.

From the ED perspective, imipenem or meropenem may be appropriate in patients with suspected serious gram-negative infections that are healthcare associated. In particular, patients with recent prolonged hospitalization (especially in an intensive care unit [ICU]) may be at risk of infections requiring empiric use of imipenem or meropenem. Ertapenem is appropriate in some patients with diabetic foot infection, pneumonia, or complicated UTI.

The carbapenems are time-dependent killers. Unfortunately, they are typically not stable in solution for 24 hours, therefore prohibiting use in continuous infusion. However, studies have been performed on extended infusions (eg, each dose given over 3 or 4 hours), which represents a theoretical advantage over conventional dosing (whereby each dose is infused over 30 minutes).

Carbapenem use may occasionally be associated with the development of seizures. This adverse effect typically occurs in patients with a past history of neurologic abnormalities and in whom appropriate dose adjustment has not occurred in the presence of renal impairment.

FLUOROQUINOLONES

The fluoroquinolones include ciprofloxacin, levofloxacin, and moxifloxacin. They have differences in spectrum, which are described in Table 4:

Practice Pearl

Try to avoid quinolones in competitive athletes because of the risk of tendon rupture.

The fact that ciprofloxacin does not cover *S pneumoniae* well rules this antibiotic out as a suitable treatment for community-acquired respiratory tract infections. However, both levofloxacin and moxifloxacin do provide adequate coverage of *S pneumoniae* and are therefore potentially useful for therapy of infections such as CAP. Both ciprofloxacin and levofloxacin have activity against the gram-negative pathogens that are typical causes of UTI and have a long history of successful use for this condition. However, it must be pointed out that resistance of *E coli* to the quinolones is increasing substantially. Resistance of *P aeruginosa* to quinolones is also substantial in some ICUs, potentially limiting the use of ciprofloxacin or levofloxacin in treatment of pneumonia potentially due to *P aeruginosa*. Moxifloxacin has coverage against most of the organisms responsible for complicated intra-abdominal infections so may be of use if patients have allergies to more commonly prescribed agents for this condition.

The fluoroquinolones mentioned above have both oral and IV formulations. The quinolones are well absorbed from the upper GI tract. Their oral bioavailability exceeds 50% for all and some such as levofloxacin have a bioavailability of approximately 90% or greater. When administered IV, it is not appropriate to use the fluoroquinolones as a continuous or extended interval infusion. The use of fluoroquinolones has been linked to *C difficile*–associated diarrhea. Occasionally, patients receiving fluoroquinolones develop neurotoxicity, especially if doses are not adjusted in the presence of renal dysfunction. Achilles tendon rupture has been associated with fluoroquinolone use.

Practice Pearl

Whenever possible, fluoroquinolones should be administered orally, since the drugs, as a class, have excellent bioavailability.

MACROLIDES AND KETOLIDES

Commonly used macrolide antibiotics include azithromycin and clarithromycin. Erythromycin is rarely used for its antimicrobial activity. Telithromycin is the only commercially available ketolide, while cethromycin is in advanced clinical development. The macrolides and ketolides have greatest clinical utility in treatment of community-acquired respiratory tract infections because they have in vitro activity against both *S pneumoniae* and the "atypical" agents of respiratory infection (*Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*). There are now substantial rates of resistance of

Table 4. The Fluoroquinolones

	S pneumoniae	*Enterobacteriaceae* (such as those causing UTI)	P *aeruginosa*	Anaerobes
Ciprofloxacin	-	++	++	-
Levofloxacin	+++	++	++	-
Moxifloxacin	+++	++	+	+++

S pneumoniae to the macrolides. Therefore, in treatment of CAP, physicians are advised to combine the macrolide with a highly potent antipneumococcal agent such as ceftriaxone.

Use of the macrolides may be associated with gastrointestinal side effects. Both macrolides and ketolides may be associated with a prolonged QT interval. The ketolides have been associated with hepatotoxicity and exacerbations of myasthenia gravis.

Practice Pearl

Macrolides have been shown not to be useful in healthy adults with acute bronchitis.

VANCOMYCIN, DAPTOMYCIN, AND LINEZOLID

Although members of 3 different classes, vancomycin, daptomycin, and linezolid share a common feature: they are all active against gram-positive cocci without having any significant activity against gram-negative bacilli.

VANCOMYCIN

Vancomycin, a glycopeptide antibiotic, has activity against *S pneumoniae*, including penicillin- or ceftriaxone-resistant strains. Therefore, it plays a role for the ED physician as part of empiric therapy for meningitis (in combination with ceftriaxone), since *S pneumoniae* is a common cause of bacterial meningitis.

Vancomycin has been the drug of choice for MRSA infections for many years but is now being recognized as having significant issues. Predominant among these is that its large size makes diffusion into lung tissue difficult. As a result, pulmonary concentrations are approximately one sixth of blood concentrations. There are a number of lines of evidence suggesting that this results in suboptimal therapy of patients with MRSA pneumonia. Vancomycin remains a useful drug for skin and soft tissue infections due to MRSA or due to more susceptible organisms in patients with allergies to beta-lactam antibiotics.

Practice Pearl

Vancomycin is inferior to antistaphylococcal penicillins (like nafcillin) for MSSA. When treating infections with S aureus, use vancomycin only for suspected or confirmed MRSA infections or in patients with penicillin allergy.

Dosing of vancomycin has been traditionally commenced at 1 g q12h IV in patients with normal renal function. However, there has been a trend to use higher doses (eg, 15 mg/kg q12h) in patients with serious MRSA infections such as complicated bloodstream infection. It has not yet been determined whether this is associated with an increased risk of adverse effects. When given orally, vancomycin remains in the gut lumen. As a result, the drug does not get absorbed into the bloodstream and is ineffective for infections other than those involving the gut.

Vancomycin can cause an infusion reaction ("red man syndrome") when given too rapidly. As a result, infusions are typically of 1-hour duration. Renal toxicity may occur with vancomycin, particularly when co-administered with gentamicin. However, the risk of nephrotoxicity with vancomycin monotherapy is quite low. As a result, it has been suggested that vancomycin blood concentrations only be measured in patients with changing renal function. Typically, a trough level (predose blood concentration) is the only level collected. The aim for most infections is a trough level of 10–20 mg/L.

There are fewer than 10 reported cases of vancomycin resistance in *S aureus*. However, greater numbers of "heteroresistance" or vancomycin intermediate *S aureus* infections have been described, particularly after prolonged therapy. Methicillin-resistant *Staphylococcus epidermidis* strains with reduced susceptibility to vancomycin have also been described. Vancomycin-resistant enterococci (VRE) are endemic in many large medical centers. The availability of linezolid, daptomycin, and tigecycline has facilitated VRE therapy.

DAPTOMYCIN

Daptomycin is a lipopeptide antibiotic. Like vancomycin it has activity against MRSA. However, in addition to anti-MRSA activity, it is typically active against VRE. Daptomycin is indicated in the therapy of skin and soft tissue infections and *S aureus* bloodstream infection. In a study of patients with CAP, daptomycin was found to be inferior to ceftriaxone. It was subsequently found that daptomycin is inactivated by surfactant, thereby rendering the drug useless in therapy of pulmonary infections.

Practice Pearl

The only place for oral vancomycin is for therapy of C difficile colitis.

Daptomycin has utility in outpatient management of skin and soft tissue infections because it can be administered once a day. (The usual dose for these infections in patients with normal renal function is 4 mg/kg q24h.) Thus, there is an advantage over vancomycin, which needs twice-daily administration.

Daptomycin also has potential utility in inpatient management of complicated MRSA bloodstream infection, including infective endocarditis. However, it must be stressed that MRSA endocarditis is associated with substantial mortality. Typically, removal of infected intravascular devices and valvular replacement is necessary to cure MRSA endocarditis. Development of MRSA resistance to daptomycin has been recorded in patients in whom foreign bodies could not be removed.

Daptomycin is typically very well tolerated. Creatine phosphokinase (CPK) elevation is seen in a small proportion of patients treated with the drug.

LINEZOLID

Linezolid is the first of a new class of antimicrobial agents known as the oxazolidinones. Like vancomycin and daptomycin, it has activity solely against gram-positive organisms such as MRSA and VRE. The drug is potentially useful for therapy of skin and soft tissue infections and pulmonary infections where MRSA is suspected. A major advantage of the drug is that it is available in both IV and orally administered forms. The dose for both formulations is 600 mg q12h. There is no need to alter the dose in patients with renal dysfunction.

Linezolid penetrates pulmonary tissue well and is not inactivated by surfactant. Therefore, it has potential advantages over vancomycin and daptomycin in the therapy of MRSA pneumonia. Some studies have suggested a survival advantage of linezolid vs vancomycin (dosed at 1 g q12h) in the therapy of MRSA pneumonia. Linezolid is bacteriostatic and not recommended for treatment of bloodstream infection.

The oral availability of linezolid for therapy of MRSA skin and soft tissue infections presents opportunities but also potential problems. Community-acquired MRSA strains are frequently susceptible to trimethoprim/sulfamethoxazole (Bactrim™) or clindamycin. Both of these antibiotics are substantially less expensive than linezolid. Some significant toxicities have been observed with linezolid. Foremost among these is bone marrow suppression. Thrombocytopenia or neutropenia associated with linezolid typically occur after 10–14 days' therapy. As a result, patients on prolonged linezolid should have a full blood count determined at least once weekly. Rare but devastating complications of linezolid therapy have been described, which include lactic acidosis, optic neuritis, and peripheral neuropathy.

Tetracyclines and Tigecycline

TETRACYCLINES

Tetracycline and related antibiotics (doxycycline and minocycline) have activity against a variety of pathogens but find most use in therapy of acne and against "atypical" pathogens such as Rickettsia spp. Doxycycline is a recommended option for outpatient treatment of CAP, since it has activity against organisms such as *M pneumoniae*, *C pneumoniae*, and *S pneumoniae*. Tetracyclines should be avoided in pregnancy and in children.

Practice Pearl

Doxycycline 100 mg twice a day is a useful option for the patient being discharged from the ED with community acquired respiratory infection.

TIGECYCLINE

Tigecycline is a glycylcycline, a class related to the tetracyclines. Tigecycline is indicated for the treatment of complicated skin and soft tissue infections and intra-abdominal infections. Successful trials of tigecycline in the therapy of CAP have also been completed. Tigecycline has in vitro activity against MRSA, VRE, *S pneumoniae*, many gram-negative bacilli (with notable exceptions including *P aeruginosa* and *Proteus* spp.) and anaerobes such as *B fragilis*. The activity against *S aureus* explains tigecycline's potential utility for skin and soft tissue infections. Tigecycline's activity against enterococci, most gram-negative bacilli, and anaerobes explains the drug's potential utility for intra-abdominal infections.

Tigecycline is only available in an IV formulation. The drug has unusual pharmacokinetics in that blood concentrations are low, but most tissue concentrations are much higher. Therefore, concerns have been raised about use of tigecycline in treatment of bloodstream infections. The antibiotic undergoes little elimination into the urine and is therefore not recommended for use in UTIs. Dose adjustment is not needed in renal dysfunction.

Tigecycline retains in vitro activity against most strains of *A baumannii*, a common cause of ICU-acquired infection, especially pneumonia. *A baumannii* may be resistant to all antibiotics except tigecycline and colistin, raising hopes that the drug may be of use for multiresistant infections caused by this infection. Unfortunately, tigecycline has been found to be inferior to imipenem in the treatment of HAP. Therefore, tigecycline should be reserved as second-line therapy for *A baumannii* infections such as pneumonia.

Tigecycline use has been associated with significant rates of nausea and vomiting. However, many patients receiving the antibiotic will be sedated and ventilated in ICUs, making these gastrointestinal side effects less of an issue. Other adverse effects of tigecycline therapy are uncommon.

AMINOGLYCOSIDES

Gentamicin, tobramycin, and amikacin represent the most important examples of the aminoglycoside class. These antibiotics would be used by ED physicians in the following contexts:

- Empiric therapy of serious UTIs such as acute pyelonephritis. This may be as monotherapy.
- Empiric therapy of suspected serious gram-negative bacterial infections requiring admission to ICU. This must be as part of combination therapy.
- Pathogen-directed therapy for suspected or proven staphylococcal, streptococcal, or enterococcal bloodstream infection (especially complicating endocarditis). This will always be part of a combination antibiotic regimen with a beta-lactam or vancomycin and will typically be under the direction of an infectious diseases physician.

Although aminoglycosides may be administered by the respiratory route, most ED-initiated aminoglycoside therapy will be IV. The aminoglycosides are concentration-dependent killers, implying a mechanistic basis for the current trend to use higher doses less frequently. Doses of 5–7 mg/kg q24h (for gentamicin and tobramycin) are currently recommended for serious gram-negative infections in patients with normal renal function. A single dose of 5–7 mg/kg (of gentamicin or tobramycin) is appropriate for patients with renal dysfunction; subsequent doses can be given when the blood concentration falls below 1 mg/L.

Many physicians are concerned about the toxicity of aminoglycosides. The most important modifiable determinant of toxicity is duration of therapy. Patients receiving aminoglycosides for >2 weeks have a 50% risk of toxicity. In contrast, those receiving these antibiotics for <1 week have a risk of toxicity of <5%. Therefore, it is safe for ED physicians to commence aminoglycosides (best prescribed as a single dose) in the vast majority of patients in which these antibiotics are indicated.

Practice Pearl

Gentamicin 5 mg/kg as an initial single antibiotic dose is a useful alternative to quinolones in the healthy young woman with acute pyelonephritis.

METRONIDAZOLE

Metronidazole has significant activity against anaerobic bacteria and against some protozoa (eg, *Giardia lamblia* or *Entamoeba histolytica*). ED physicians may potentially use this antibiotic in patients with the following:

- Suspected *C difficile* diarrhea
- Peritonitis (in combination with an antibiotic active against aerobic gram-negative bacilli)
- Suspected giardiasis or amebiasis

Practice Pearl

Advise the patient to avoid any use of alcohol when taking metronidazole.

FOLIC ACID ANTAGONISTS

Trimethoprim has activity against pathogens causing UTI such as *E coli*. The addition of sulfamethoxazole gives synergistic activity against some gram-negative bacilli and against *S aureus*. A major adverse reaction of trimethoprim/sulfamethoxazole (Bactrim™) is rash, including the potential for Stevens-Johnson syndrome.

Practice Pearl

Trimethoprim/sulfamethoxazole has excellent activity against S aureus, including many strains of community-acquired MRSA. However, the drug combination lacks activity against S pyogenes (Group A Streptococcus). Therefore, trimethoprim/sulfamethoxazole is a good therapy for infections such as carbuncles or abscesses (where S aureus predominates), but may not be an optimal therapy for cellulitis (where S pyogenes predominates).

ED physicians may potentially use trimethoprim/sulfamethoxazole in patients with the following:

- UTI
- Skin and soft tissue infections suspected as being due to MRSA
- Prophylaxis and treatment of *Pneumocystis* pneumonia (PCP)

CLINDAMYCIN AND LINCOMYCIN

Clindamycin and lincomycin have activity against gram-positive organisms and anaerobic organisms but not against aerobic gram-negative organisms. Clindamycin has activity against *S aureus* and *S pyogenes*. Clindamycin use has been associated with *C difficile*–associated diarrhea.

Clindamycin is potentially useful to the ED physician in the following:

- Skin and soft tissue infections suspected as being due to MRSA
- Skin and soft tissue infections in patients allergic to penicillins or cephalosporins
- Aspiration pneumonia or diabetic foot infection, but only when combined with an agent active against gram-negative bacilli (eg, a fluoroquinolone or an aminoglycoside)

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Practice Pearl

Clindamycin-resistance can be induced in some strains of MRSA. This potential should be considered whenever the initial antibiotic susceptibility pattern of the organism shows sensitivity to clindamycin but resistance to erythromycin. Clinical microbiology laboratories will evaluate the potential for inducible resistance by performing a "D-test" when this pattern is seen. Until the results are available, however, caution is advised.