Maximizing Therapeutic Success in an Era of Increasing Antibiotic Drug Resistance

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Target Audience

This activity is intended for infectious disease specialists, internists, and other physicians and healthcare professionals who treat infected patients with parenteral antibiotics in hospitals and intensive care units as well as nurses who work in hospitals and healthcare facilities where serious bacterial infections are treated with parenteral agents.

Goal

The goal of this activity is to provide a strategy to optimize antibiotic use, including defining the role of newer antibiotic options in treating serious hospital infections caused by emerging gram-negative and gram-positive pathogens.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Review current data in regard to the prevalence, clinical impact, and management challenges of antimicrobial drug resistance in hospital settings.
2. Use expert recommendations concerning antibiotic selection and use for empiric therapy to determine optimum antibiotics in clinical practice.
3. Appropriately incorporate both older and newer antibiotics in the management of serious bacterial infections, particularly those encountered in hospital settings.

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Maximizing Therapeutic Success in an Era of Increasing Antibiotic Drug Resistance

Introduction

Resistance of bacteria to antibiotics has been noted ever since the discovery of penicillin by Fleming and its subsequent production by Florey. Antibiotic resistance may be intrinsic: This implies that the antibiotic is unable to have an effect on "wild-type" bacteria previously unexposed to the antibiotic in question. For example, vancomycin is not active against gram-negative bacteria, nor has it ever been. Antibiotic resistance may also be either mutational or acquired. This implies changes in the bacteria that prevent the antibiotic from exerting its effect on the bacterial target, which may have resulted from either (1) mutation of existing genetic material within the bacteria or (2) acquisition of new genetic material from other bacteria. For example, Escherichia coli in its natural state may be susceptible to both ampicillin and ciprofloxacin. However, the mutation of existing genetic material may lead to ciprofloxacin resistance, and the acquisition of genes that encode for beta-lactamase production may lead to resistance of E coli to ampicillin.

The problems of antibiotic resistance are typically magnified in a hospital setting. Exposure to antibiotics while a patient is in the hospital may lead to genetic mutations that contribute to antibiotic resistance. Patients may be inadvertently exposed to the bacterial flora of other patients (usually due to a breakdown in basic infection control precautions). As a result, antibiotic-resistant bacteria may colonize multiple patients: Exposure of these patients to antibiotics may eliminate all but the most resistant bacteria. These resistant organisms may transfer antibiotic resistance genes to other bacteria, thereby multiplying the problem.

Antibiotic resistance is therefore a major issue for clinicians, but especially those who practice in hospital settings. This Clinical Update concentrates on 3 areas: (1) current data in regard to the prevalence of antibiotic resistance in the hospital setting, (2) recommendations in regard to antibiotic selection for specific pathogens, and (3) recommendations in regard to empiric antibiotic selection for common serious infections.
1. How do the rates of antibiotic resistance at your institution compare with national or international averages?
- Lower in general
- About the same
- Higher in general

**Explanation:**
One of the 3 is probably true, depending on the type of institution (teaching or community, for example).

2. Which of the following is the most important barrier in the optimal management of a patient with nosocomial infection? (Select 1 answer.)
- Lack of effective treatment options for multidrug-resistant pathogens
- Lack of hospital-specific cumulative antibiotic susceptibility report
- Lack of unit-specific cumulative antibiotic susceptibility report
- Patient's comorbidities

3. How confident are you that you are up-to-date in the optimal management of nosocomial infections? (Select 1 answer.)
- Not at all confident
- Somewhat confident
- Confident
- Very confident
4. How do you use knowledge of local rates of resistance in choosing antibiotic therapy for a patient with a life-threatening infection?

- Follow published treatment guidelines
- Follow hospital treatment protocols
- Initiate broad-spectrum antibiotic regimen and de-escalate when possible
- Initiate narrow-spectrum antibiotic regimen and add antibiotics as necessary
- Individualize treatment

**Explanation:**
"Individualize treatment" is the most politically correct answer; however, both "Follow hospital treatment protocols" and "Initiate broad-spectrum antibiotic regimen and de-escalate when possible" are also appropriate responses.

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**The Prevalence of Antibiotic Resistance in the Hospital Setting**

All of us who work in the hospital setting understand that antibiotic resistance is an important issue. However, the epidemiology of antibiotic-resistant organisms varies from one geographic area to another. Furthermore, even in an individual hospital, there is variation in the occurrence of resistant organisms.

**The Unit-Specific or Hospital-Specific Cumulative Antibiotic Susceptibility Report or "Antibiogram"**

For any individual patient with an infection, an antibiotic susceptibility report is typically issued, detailing the susceptibility of the particular organism to multiple antibiotics. In an individual institution or a unit within that institution, cumulative antibiotic susceptibility reports on multiple patients ("antibiograms") can be constructed in order to aid with appropriate antibiotic choice.

Antibiotic use can be classified into 4 categories (Table 1). First, antibiotic use may be prophylactic, such as in the perioperative use of antibiotics to prevent surgical wound infection. Second, antibiotics may be used as empiric treatment. This implies the use of antibiotics directed at a particular syndrome -- such as community-acquired urinary tract infection or ventilator-associated pneumonia -- without precise knowledge of the
organisms causing the infection. Third, antibiotic use may be pathogen-directed. In other words, the organism causing the infection (for example, Staphylococcus aureus) is known, but the susceptibility of the organism is unknown. Finally, antibiotic therapy may be susceptibility-guided. In this case, both the identity of the organism causing infection and the susceptibility profile of the organism are known.

Table 1. Types of Antibiotic Therapy and How Antibiograms Can Assist in Choice of Therapy

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Description</th>
<th>Use of Antibiograms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Antibiotics used to prevent infection</td>
<td>Selection of antibiotic</td>
</tr>
<tr>
<td>Empiric</td>
<td>Organism is unknown but syndrome is known</td>
<td>Selection of antibiotic or combinations of antibiotics</td>
</tr>
<tr>
<td>Pathogen-directed</td>
<td>Organism is known but susceptibility is unknown</td>
<td>Selection of antibiotic</td>
</tr>
<tr>
<td>Susceptibility-guided</td>
<td>Organism is known and susceptibility is known</td>
<td>Cumulative antibiogram not useful</td>
</tr>
</tbody>
</table>

The provision of cumulative antibiotic susceptibility reports (antibiograms) is particularly helpful for choosing empiric and pathogen-directed treatment regimens. In contrast, the provision of antibiotic susceptibility reports on individual patients is clearly of use to ensure that antimicrobial treatment was adequate for the organism causing the infection. It also assists in antibiotic "streamlining" -- the process by which excessively broad-spectrum empiric antibiotic therapy can be switched to narrower spectrum therapy aimed only at the implicated pathogen(s).

Cumulative Antibiotic Susceptibility Reports and Choice of Empiric Therapy

A major role for cumulative antibiotic susceptibility reports is in guiding antibiotic choice for empiric therapy. A large proportion of antibiotic therapy is empiric, be it antibiotic therapy commenced in the community or in the hospital. In most circumstances, the clinician will make a diagnosis of the anatomic site of infection on the basis of the patient's symptoms and signs. In some circumstances, additional laboratory tests or radiologic studies will be needed in order to make the diagnosis. Thus, a clinician may diagnose conditions, such as uncomplicated urinary tract infection, community-acquired pneumonia, late-onset ventilator-associated pneumonia, etc. Because empiric therapy occurs in the absence of knowledge of the organism causing the infection, the choice of antibiotics rests on the likely organisms causing that particular type of infection. For example, for uncomplicated urinary tract infection, E coli predominates; for community-acquired pneumonia, Streptococcus pneumoniae; and for ventilator-associated pneumonia, Pseudomonas aeruginosa, S aureus, Enterobacter cloacae, and Klebsiella pneumoniae are most frequently isolated.
Empiric antibiotic therapy that is based on an antibiogram is most likely to be helpful when the antibiogram closely reflects the source of organisms in the patient. Thus, an antibiogram for community-acquired *E coli* isolates from women with uncomplicated urinary tract infection is more likely to be useful in guiding therapy for an individual patient with uncomplicated urinary tract infection than is a hospital antibiogram for *E coli*. The geographic source of organisms is also relevant. Thus, an antibiogram for *S pneumoniae* isolates produced by the Georgia State Department of Health is of questionable relevance in treating an individual patient with community-acquired pneumonia in Boston, Massachusetts. This is the important question that this issue raises: "How can clinicians obtain antibiograms that are meaningful to their patients?"

Laboratories processing specimens from outpatients rarely produce antibiograms. Furthermore, it may be difficult for such laboratories to distinguish whether samples are from patients in nursing homes or truly from the community. This is important because antibiotic pressures and infection control considerations are likely to lead to a greater extent of antibiotic resistance in nursing homes than elsewhere in the community.

Important issues also arise for the hospital clinical microbiology laboratory constructing an antibiogram. It may be difficult for a microbiologist to determine whether organisms are community-acquired or hospital-acquired. Hospital laboratories should know the ward in which the patient was residing at the time when the isolate was collected. This, however, may not be the source of the infection. For example, a patient admitted from home to a medical intensive care unit (ICU) with sepsis of urinary tract origin may actually have a community-acquired pathogen rather than an ICU-acquired pathogen. Isolates from patients in emergency departments of tertiary care referral centers may be particularly misleading. For example, it may be tempting to assess the advent of community-acquired methicillin-resistant *S aureus* (MRSA) in a particular locality by determining the proportion of oxacillin resistance in *S aureus* isolates collected from patients in the hospital's emergency department. However, this may be grossly misleading because more than 50% of such isolates may be from patients with recent hospital admission and discharge, who are representing to the hospital with complications.

Despite these caveats, antibiograms can potentially provide useful information for antibiotic prescribers. It is known that for patients in ICUs, mortality rises if the empiric antibiotic therapy chosen does not cover the pathogens causing the infection.[1-4] Kollef and colleagues[1] showed that infection-related mortality was 17.7% in those patients who received appropriate empiric antibiotic therapy vs 42.0% in those patients who received inappropriate empiric antibiotic therapy. The most common reason why empiric antibiotic therapy was inappropriate was resistance of the bacteria to the antibiotic chosen. In an effort to improve the adequacy of their antibiotic selection, Ibrahim and colleagues[5] reviewed the antibiogram for their particular ICU and created a clinical guideline for antibiotic selection in that unit. The adequacy of empiric antibiotic selection for ventilator-associated pneumonia for patients in their ICU increased from 48.0% before the creation of antibiotic guidelines to 94.2% with the use of their guidelines.
It must be acknowledged that an antibiogram-based guideline does not have an unlimited duration of utility. It is likely that shifts in antibiotic usage engendered by the creation of the guideline will, over time, lead to a change in resistance patterns. Thus, it is prudent to update antibiograms and antibiogram-based antibiotic guidelines on a regular basis. A yearly review should be regarded as a bare minimum. "Rolling" antibiograms, which are constantly updated, are probably optimal if an institution has the information technology resources to create them.

An important consideration is whether hospital-wide antibiograms give an accurate indication of antibiotic resistance in a particular unit within the hospital. Namias and colleagues[6] showed that ICU antibiograms differed substantially from the antibiogram for the entire hospital. I have observed a similar finding in my own institution: A recent antibiogram for the entire hospital showed that 69% of *P aeruginosa* isolates were susceptible to gentamicin, whereas just 34% of such isolates from one particular ICU were susceptible to gentamicin. In contrast, in another ICU in my hospital, 79% of *P aeruginosa* isolates were susceptible to gentamicin. It appears important for prescribers in ICUs to request unit-specific antibiograms so that empiric antibiotic prescribing can be optimized.

Even in such ICUs, care needs to be exercised when extrapolating recommendations from unit-specific antibiograms to specific patients. Some patients have a long duration of stay in ICUs, during which time they have colonization with multiply resistant organisms and receive therapy with multiple antibiotics. El Amari and colleagues[7] found that the greatest risk factor for antibiotic resistance in *P aeruginosa* was prior use of the particular antibiotic to which the organism is known to be resistant. Thus, in patients with prolonged ICU stay (arbitrarily defined as ICU length of stay exceeding 14 days), empiric therapy may better be individualized on the basis of avoidance of antibiotics that the patient has previously received. A second principle is avoidance of antibiotics to which colonizing organisms are known to be resistant.

A frequently raised issue concerns the level of resistance that should denote that a particular antibiotic should be avoided as empiric therapy. Opinions about this vary widely. For example, in the empiric treatment of gonorrhoea, it is often stated that an antibiotic should not be used empirically if there is greater than 5% resistance to that particular antibiotic in *Neisseria gonorrhoeae* strains from that community.[8] Such a standard would never be practical for many hospital-acquired organisms. For example, in many hospitals *P aeruginosa* strains have, cumulatively, greater than 5% resistance to every antibiotic. The most scientifically valid way to assess this situation is to perform a decision analysis. Information required to perform such an analysis includes the consequences of empiric therapy to which the organism is found to be either susceptible or resistant. It is well known that not all patients treated with an antibiotic to which the organism is resistant will do poorly, nor will every patient treated with an antibiotic to which an organism is susceptible do well.[9] A decision analysis assigns literature-based probabilities for various outcomes and often assigns costs to various outcomes. An example is that of Le and Miller[10] who showed that when more than 22% of *E coli* urinary isolates in a community are resistant to trimethoprim-sulfamethoxazole (TMP-
SMX), empiric quinolone therapy for uncomplicated urinary tract infection becomes less costly than TMP-SMX.

Studies such as this are lacking for hospital-acquired infections. In general, unit-specific hospital antibiograms serve more utility in showing which antibiotics should be avoided for specific infections rather than which antibiotics should be used. For example, if cumulative susceptibilities for \textit{P. aeruginosa} in a particular ICU are meropenem 82\%, cefepime 80\%, piperacillin-tazobactam 79\%, and aztreonam 50\%, it would be logical to exclude aztreonam as an empiric antibiotic choice for patients with suspected pseudomonal infections. Such susceptibilities may not distinguish between meropenem, cefepime, and piperacillin-tazobactam as a treatment of choice. However, they do serve as an indication that combination beta-lactam/aminoglycoside or beta-lactam/quinolone therapy be used empirically, because even the most active antibiotic lacks activity against a substantial proportion of strains.

**Cumulative Antibiotic Susceptibility Reports and Choice of Pathogen-Directed Therapy**

In many situations, the identification of the infecting bacterial pathogen will be known before the antibiotic susceptibility results. Usually the delay is just 24 hours, but this may represent an important window for optimization of antibiotic therapy in critically ill patients. There is therefore an opportunity for clinical microbiology laboratories to work with providers to develop pathogen-specific guidelines. Thus, if a clinician receives a report that a patient has \textit{E. cloacae} growing in a particular specimen, then a reasoned antibiotic choice could be made for that patient by consulting with a unit-based antibiogram. An example of such a pathogen-specific guideline is given in Table 2 and in the following list: \[^{11-15}\]

- **Recommendations for treatment of \textit{Enterobacter} infections when susceptibilities are not yet available:**
  - Bacteremia -- cefepime 1 g every 12 hours intravenously (IV) or levofloxacin 500 mg every 24 hours IV
  - Pneumonia -- cefepime 1 g every 12 hours IV or levofloxacin 500 mg every 24 hours IV
  - Urinary tract infection -- TMP-SMX (3 mg/kg per dose of the TMP component every 8 hours) or 1 double-strength tablet every 12 hours by mouth
- **Role of combination therapy:** Two large studies of serious \textit{Enterobacter} infections have been performed. In neither study did combination therapy result in a significant improvement in survival or a reduction in emergence of resistance
• Therapy once susceptibilities are known: Streamlining to TMP-SMX should be performed: The drug is inexpensive and has yielded excellent results in the treatment of serious *Enterobacter* infections.

Third-generation cephalosporins (eg, ceftriaxone, cefotaxime, and ceftazidime) should be avoided in serious *Enterobacter* infections, regardless of apparent in vitro susceptibility, because there is a significant risk for relapse of infection.

**Table 2. An Example of a Pathogen-Directed, Unit-Specific Antibiogram**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of Isolates</th>
<th>ICU Percentage Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin-sulbactam</td>
<td>58</td>
<td>32.7</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>54</td>
<td>64.8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>58</td>
<td>98.3</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>56</td>
<td>62.5</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>57</td>
<td>50.9</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>56</td>
<td>98.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>58</td>
<td>91.4</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>56</td>
<td>71.5</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>58</td>
<td>96.6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>58</td>
<td>74.1</td>
</tr>
</tbody>
</table>

*ICU = intensive care unit; TMP-SMX = trimethoprim-sulfamethoxazole*

*This antibiogram represents Enterobacter cloacae, Enterobacter aerogenes, and other rarer species combined. E aerogenes is more likely to be susceptible to some antibiotics than E cloacae.*

Such an antibiogram can be posted on the Web site of an ICU or be part of a guidelines booklet for an institution or unit.

**National and International Data on the Extent of Antibiotic Resistance**

In some institutions, antibiograms are not available. In this instance, it is necessary to obtain national data sets to determine the most likely extent of antibiotic resistance of a particular bacterial pathogen. Even if antibiograms are produced by a particular institution, it is useful to review national data for 2 reasons. First, it allows for a comparison of local data with national data to determine whether the extent of resistance is better or worse than national averages. Second, it provides the ability to presage future trends in antibiotic resistance: If resistance is rising for a particular pathogen at a national level, it may be only a matter of time before resistance rates rise locally.
Data on antibiotic resistance in the United States are collected by the US Centers for Disease Control and Prevention (CDC) via the National Nosocomial Infections Surveillance (NNIS) System. This system was established in 1970 when selected hospitals in the United States began to routinely report their nosocomial infection surveillance data for aggregation into a national database. Nearly 300 hospitals participate in the NNIS System. The NNIS data presented here are predominantly from patients in ICUs.

With regard to gram-positive organisms, 28.5% of enterococci associated with nosocomial infections in ICU patients in 2003 were resistant to vancomycin. This represented a 12% increase compared with aggregate data from 1998 to 2002. About 59.5% of \textit{S. aureus} strains and 89.1% of coagulase-negative staphylococci from the same study were methicillin-resistant. This represented an 11% increase in methicillin resistance in \textit{S. aureus} compared with 1998-2002. Clearly, MRSA is a substantial problem that necessitates the use of alternative antibiotics, such as vancomycin, linezolid, daptomycin, or tigecycline, in many clinical situations. This is discussed in greater detail in subsequent sections.

The greatest extent of increase in resistance of any organism to antibiotics was "resistance" of \textit{K. pneumoniae} to third-generation cephalosporins. Resistance of \textit{K. pneumoniae} or \textit{E. coli} to third-generation cephalosporins is actually defined as nonsusceptibility to either aztreonam or third-generation cephalosporins, and is a surrogate marker for the production of extended-spectrum beta lactamases (ESBLs). These beta lactamases are a major threat to the routine use of cephalosporins and penicillins. Over one fifth (20.6%) of \textit{K. pneumoniae} strains associated with nosocomial infections in ICU patients in 2003 were nonsusceptible to either aztreonam or third-generation cephalosporins: This represented a 47% increase compared with aggregate data from the 5 previous years. In contrast, just 5.8% of \textit{E. coli} strains were nonsusceptible to aztreonam or third-generation cephalosporins. Resistance of \textit{Enterobacter} strains to third-generation cephalosporins, exhibited by 31.1% of strains in 2003, is a marker of hyperproduction of the AmpC beta lactamase. This beta lactamase, which differs structurally from ESBLs, is an important mechanism of resistance to cephalosporins and penicillins of \textit{Enterobacter} species, \textit{Serratia} species, \textit{Citrobacter} species, and other related organisms.

\textit{P. aeruginosa} is an important pathogen that is associated with hospital-acquired infections. Unfortunately, the organism is notable for intrinsic resistance to multiple antibiotics plus the ability to develop mutational resistance or acquire new mechanisms of resistance. Resistance of an individual \textit{P. aeruginosa} strain to multiple antibiotics is frequently encountered. In the NNIS System survey in 2003, the resistance rates of \textit{P. aeruginosa} were 31.9% (to ceftazidime), 29.5% (to quinolones), and 21.1% (to imipenem). The NNIS System has not published rates of resistance of \textit{Acinetobacter} species or \textit{Stenotrophomonas maltophilia}; however, these organisms are also notable for their intrinsic, mutational, and acquired mechanisms of resistance to multiple antibiotics.
5. Which of the following antibiotics would you consider first-line for therapy of serious infections due to *E coli*, *Klebsiella* species, or *Enterobacter* species?

- Ertapenem
- Imipenem-cilastatin
- Levofloxacin
- Linezolid
- Tigecycline

**Explanation:**
It depends on the hospital. At a teaching hospital, imipenem, ertapenem, and tigecycline are appropriate choices. At a community hospital, levofloxacin would be acceptable. The broad-spectrum coverage of imipenem is not necessary for these pathogens, and linezolid does not cover gram negatives, such as those listed.

**Antibiotic Selection for Specific Pathogens**

*S aureus*

As previously noted, the prevalence of MRSA in hospital-acquired infections is high. Community-acquired MRSA is also on the increase, and may be "imported" into hospitals. If *S aureus* isolates are methicillin-susceptible, then semisynthetic penicillins, such as nafcillin or oxacillin, should be used in preference to alternative agents. For many years, vancomycin has been regarded as the treatment of choice for MRSA infections. However, there are concerns that outcomes with vancomycin are not as favorable as could be potentially achieved with newer alternative agents (linezolid, daptomycin, or tigecycline). It is probable that the conventional vancomycin dosing regimen of 1 g every 12 hours IV is inadequate for infection types, such as pneumonia or bloodstream infection related to endocarditis, osteomyelitis, or other deep-tissue sites. In such situations, I would suggest aiming for vancomycin trough levels of at least 15-20 mcg/mL or mg/L. Whether these levels are best achieved by continuous infusion or intermittent infusion at a higher dose is a matter of debate. A randomized trial of continuous-infusion vancomycin (target serum concentration, 20-25 mg/L) vs
intermittent infusion (target trough, 10-15 mg/L) has been performed. Persistent bacteremia after 5 days was lower in the continuous-infusion group than in the every 12 hours group (28% vs 35%), but the sample size was too small (119 total) to adequately determine whether this was a statistically significant difference.

Alternatives to vancomycin for MRSA infections include linezolid, daptomycin, and tigecycline. For methicillin-susceptible strains, all indications are semisynthetic penicillin (eg, nafcillin and oxacillin). The alternatives for MRSA are the following (doses are for patients with normal renal function):

- **Skin and soft-tissue infections:**
  - Preferred: vancomycin 1 g every 12 hours IV
  - Alternatives for outpatient therapy: linezolid 600 mg every 12 hours by mouth or daptomycin 4 mg/kg every 24 hours IV
  - Alternative for mixed infections: tigecycline 100 mg loading dose, then 50 mg every 12 hours IV

- **Pneumonia:**
  - Preferred: vancomycin 20-25 mg/kg every 12 hours IV or linezolid 600 mg every 12 hours IV
  - Alternative for mixed infections: tigecycline 100 mg loading dose, then 50 mg every 12 hours IV

- **Bacteremia:**
  - Preferred: daptomycin 6 mg/kg every 24 hours or vancomycin 20-25 mg/kg every 12 hours IV

Linezolid has potential utility for skin and soft-tissue infections treated out of hospital because both have IV and oral formulations. Linezolid has also been proven to be effective in hospital-acquired pneumonia due to MRSA. Daptomycin also has potential utility for skin and soft-tissue infections treated out of hospital because it need only be given once daily, and blood for serum concentrations does not need to be drawn. Daptomycin is rapidly bactericidal and is effective for some cases of MRSA bloodstream infection. The antibiotic is ineffective for treating pneumonia because it is inactivated by surfactant found in the lungs. Tigecycline has in vitro activity against MRSA and is effective for skin and soft-tissue and intra-abdominal infections. These infections may be polymicrobial, in which case tigecycline has an advantage over other anti-MRSA antibiotics because it has activity against a broad spectrum of gram-negative and anaerobic organisms as well. Vancomycin, linezolid, and daptomycin lack activity against gram-negative organisms.
Enterococci

The treatment of choice for serious infections, such as bacteremia due to enterococci, is ampicillin plus gentamicin if the organism is confirmed as susceptible to these antibiotics. If high-level resistance to gentamicin is found, streptomycin may be combined with ampicillin, presuming that high-level resistance to this antibiotic is not also found. Vancomycin is an alternative to ampicillin in patients with penicillin allergy. Unfortunately, vancomycin-resistant enterococci (VRE) are typically also resistant to ampicillin.

Linezolid, daptomycin, and tigecycline are all active in vitro against the majority of VRE strains. The greatest clinical experience is with linezolid; however, coinciding with the greater use of linezolid than the other alternative agents has been the advent of linezolid resistance. In some institutions, 10% to 20% of VRE isolates are linezolid-resistant. There are little published data on the use of daptomycin or tigecycline for infections with VRE, although most strains are susceptible in vitro. Because most VRE infections arise from an intra-abdominal source and may be polymicrobial, tigecycline may have some utility given its concomitant activity against gram-negative bacilli and anaerobes.

Enterobacteriaceae

The members of the Enterobacteriaceae are gram-negative bacilli, which are usually resident in the gastrointestinal tract. Examples of such organisms include *E coli*, *K pneumoniae*, *E cloacae*, *Proteus mirabilis*, and *Citrobacter freundii*. In patients hospitalized in ICUs, the Enterobacteriaceae account for approximately one third of all cases of ICU-acquired pneumonia, one third of all cases of ICU-acquired urinary tract infection, and 10% to 15% of ICU-acquired bloodstream infections.[12,13] Options for treatment of the Enterobacteriaceae include beta-lactam antibiotics (penicillin; cephalosporins; carbapenems; and the monobactam, aztreonam), beta-lactam antibiotics combined with beta-lactamase inhibitors, quinolones, TMP-SMX, aminoglycosides, and tigecycline.

Beta-lactamase production is the most common mechanism of resistance of the Enterobacteriaceae to penicillins, cephalosporins, or aztreonam. The beta lactamases inactivate these antibiotics by splitting the amide bond of the antibiotic's beta-lactam ring. Over 300 different beta lactamases have been described. As mentioned previously, most strains of *Enterobacter* species, *Citrobacter* species, *Providencia* species, *Morganella morganii*, and *Serratia* species that are resistant to third-generation cephalosporins produce an AmpC beta lactamase. Characteristically, AmpC beta lactamases can inactivate first- and second-generation cephalosporins (including the cephamycins, such as cefoxitin and cefotetan) and third-generation cephalosporins. These beta lactamases are not inhibited by beta-lactamase inhibitors, such as clavulanic acid. An important characteristic of AmpC beta lactamases is that their production can be increased by exposure of the bacteria to certain antibiotics. This phenomenon is known as induction. The amount of beta-lactamase production depends on the concentration of the antibiotic and the time of exposure. Penicillin, ampicillin, most first-generation cephalosporins,
cefoxitin, and imipenem are strong inducers of AmpC beta lactamases. However, all of these antibiotics except the carbapenem will be inactivated by the AmpC beta lactamase induced.

In most populations of organisms, such as *Enterobacter* species, mutants exist that permanently hyperproduce the AmpC type 1 beta lactamase. These mutants usually occur at frequencies of $10^{-5}$ to $10^{-8}$. Their presence at this low frequency is not enough to result in frank resistance to antibiotics, such as the third-generation cephalosporins. However, there are important clinical implications of these mutants. Antibiotic therapy with agents that are not inducers of transient beta-lactamase production (for example, third-generation cephalosporins) will kill all organisms in the colony except the permanently hyperproducing mutants. These mutants therefore become the dominant population at a site of infection and lead to frank resistance to third-generation cephalosporins. This can result in the emergence of resistance during therapy.

Organisms, such as *K pneumoniae, E coli*, or *P mirabilis*, do not characteristically hyperproduce the AmpC type 1 beta lactamase. Occasionally, they may acquire plasmid-mediated AmpC beta lactamases. However, much more commonly they may acquire ESBLs. These beta lactamases have important differences compared with AmpC beta lactamases. It is not appropriate to designate the AmpC beta lactamases as ESBLs because they are not derivatives of a parent beta lactamase with more limited spectra of activity (for example, TEM or SHV beta lactamases). The ESBLs also differ from the AmpC beta lactamases in that they are not able to inactivate the cephemycins (for example, cefoxitin or cefotetan) and are inactivated in vitro by the beta-lactamase inhibitor clavulanic acid.

Given the prevalence of beta lactamases produced by the Enterobacteriaceae, I do not consider penicillins, third-generation cephalosporins, or aztreonam as appropriate first-line therapy for serious hospital-acquired infections due to these organisms. Cefepime (a fourth-generation cephalosporin) is less likely to be inactivated by ESBLs or AmpC beta lactamases than third-generation cephalosporins. However, certain ESBL types and combinations of ESBL and AmpC production by bacteria may compromise the activity of cefepime.

Piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam are examples of the combination of a beta lactam with a beta-lactamase inhibitor. The theoretical advantage of the addition of a beta-lactamase inhibitor is that this protects the beta-lactam antibiotic from the destructive effects of the beta lactamase. The beta-lactamase inhibitors in use are active against the beta lactamases produced by anaerobic organisms, such as *Bacteroides fragilis*, and many beta lactamases commonly produced by *E coli* and *K pneumoniae* as well as the penicillinases produced by *S aureus*. Thus, these antibiotics remain useful options for the treatment of Enterobacteriaceae family.

Unfortunately, multiple mechanisms of resistance may work together in producing resistance to a given class of antibiotics. The entry of any beta-lactam antibiotic into the bacterial cell is via outer membrane proteins, which function as doors through which the
antibiotics pass. These proteins may be lost, contributing to decreased entry of the antibiotic and reduced antimicrobial activity. In some sites of infection with high organism load (for example, intra-abdominal abscesses or severe cases of ventilator-associated pneumonia), the huge amounts of beta-lactamase production by a high inoculum of organisms may overcome the effects of beta-lactamase inhibitors. Finally, as noted above, the AmpC beta lactamase (produced by organisms, such as Enterobacter species) is not susceptible to the effects of beta-lactamase inhibitors, and therefore may be inherently resistant to beta-lactam/beta-lactamase inhibitor combinations.

Quinolone antibiotics, such as ciprofloxacin and levofloxacin, are usually highly active in vitro against the Enterobacteriaceae family. However, the rates of resistance appear to be rising. There is an increased probability of resistance of ESBL-producing organisms to quinolones compared with non-ESBL-producing organisms of the same species. The reasons for this co-resistance are not entirely clear. Plasmid-mediated quinolone resistance has been reported and may contribute in some cases. The usual mechanism of resistance to quinolones is mutation of the genes that encode the target enzymes (DNA gyrase and topoisomerase IV) for quinolones. Stepwise increases in resistance occur if there are mutations in one and then two of the genes encoding these enzymes. Although not yet fully characterized, alterations in outer membrane proteins coupled with active efflux pumps (which pump antibiotics out of the bacterial cell) appear to be important additional mechanisms of bacterial resistance to quinolones.

Carbapenems are often used as drugs of last resort in the treatment of serious infections due to gram-negative bacilli. Resistance of the Enterobacteriaceae to carbapenems is generally rare, but may be mediated by the combination of outer membrane protein deficiency coupled with the production of beta lactamases. Rates of resistance to ertapenem are generally higher than to imipenem or meropenem. A new type of beta lactamase, termed KPC, has become widely prevalent in Enterobacteriaceae in New York, NY, and neighboring areas. This beta lactamase leads to resistance to all carbapenems. Other geographic areas have developed problems with production by Enterobacteriaceae of metallo-beta lactamases (MBLs). Both the KPCs and MBLs may lead to resistance of these organisms to virtually all beta-lactam antibiotics. Antibiotics that do not possess a beta-lactam ring, such as polymyxins or tigecycline, may be the only therapeutic alternative in this situation.

In view of the comments above, serious infections due to the Enterobacteriaceae family should be managed with a beta lactam or quinolone antibiotic, which is active in vitro against the infecting organism. An important caveat is that ESBL-producing organisms may appear susceptible to third-generation cephalosporins (ceftazidime, cefotaxime, or ceftriaxone) or ceftazidime, yet be functionally resistant to these agents. High clinical failure rates are observed when cephalosporins are used to treat bacteremia or pneumonia due to ESBL-producing Klebsiella species or, more rarely, ESBL-producing E. coli. Carbapenems (imipenem or meropenem) are the antibiotics of choice for serious infections due to ESBL producers. Polymyxins or tigecycline may be useful for infections that are resistant to carbapenems.
A second important finding to reemphasize is that third-generation cephalosporins are associated with a significant risk for relapse of infection when used to treat AmpC-producing organisms, such as *Enterobacter* species.\textsuperscript{[22]} Again, carbapenems or quinolones are the most reliable agents against *Enterobacter* species, *Serratia* species, or *Citrobacter* species. There is no evidence that combination therapy improves outcome or reduces the advent of resistance of the Enterobacteriaceae family.

**P aeruginosa**

*P aeruginosa* is a frequent and often the most troublesome of the gram-negative bacilli. It is a particular problem as a cause of ventilator-associated pneumonia. *P aeruginosa* is also a common cause of both bloodstream infection and cholangitis. Antibiotic resistance is a major problem posed by *P aeruginosa*; the organism displays a diverse array of antibiotic resistance mechanisms.\textsuperscript{[23]} Resistance to beta-lactam antibiotics is usually, but not exclusively, mediated by beta lactamases. *P aeruginosa* produces a chromosomally encoded AmpC beta lactamase, which can hydrolyze antipseudomonal penicillins, aztreonam, and third-generation cephalosporins. Derepressed mutants grossly hyperproduce this beta lactamase. A number of acquired beta lactamases can also be produced. MBLs have been frightening because they can hydrolyze carbapenems and all other beta lactams, with the exception of aztreonam.\textsuperscript{[24]} However, the frequent presence of other beta lactamasises in these bacteria usually results in resistance to aztreonam.

The most common mechanism of carbapenem resistance is not mediated by beta lactamase, but rather is loss of OprD, which is a porin or outer membrane protein. Loss of OprD results in resistance to imipenem and reduced susceptibility (but usually not frank resistance) to meropenem. OprD may be coregulated with an efflux pump called MexEF-OprN.\textsuperscript{[23]} Use of imipenem can select for loss of OprD, but not for upregulation of the efflux pump. In contrast, use of quinolones can select for upregulation of the efflux pump and reduced OprD (resulting in resistance to both quinolones and imipenem). Frank resistance to meropenem usually requires both the loss of OprD and upregulation of an efflux pump known as MexAB-OprM.\textsuperscript{[25]}

The efflux pumps are an important mechanism of multidrug resistance, because they may confer resistance to quinolones, antipseudomonal penicillins, cephalosporins, and sometimes aminoglycosides. Tigecycline is ineffective against *P aeruginosa* because of the presence of efflux pumps. Quinolone resistance in *P aeruginosa* may also be mediated by mutations to the chromosomally mediated topoisomerases II and IV, whereas aminoglycoside resistance may be mediated by outer membrane impermeability or by aminoglycoside-modifying enzymes.

The end result of these multiple mechanisms of resistance may be *P aeruginosa* isolates resistant to all antibiotics except for the polymyxins (colistin and polymyxin B). Resistance has even been noted to these toxic antibiotics, especially when patients have received the nebulized drug for long periods of time. Prevention of *P aeruginosa* pneumonia with nebulized colistin/polymyxin B is not recommended because of the risk for infection with resistant organisms.\textsuperscript{[26]}
There has been long-standing debate over the value of combination therapy in the treatment of serious *P aeruginosa* infections. Combination therapy had been considered the mainstay of therapy for many years, but proponents of monotherapy have emerged. Much of the support for combination therapy emanated from the study by Hilf and colleagues.\[^{27}\] In a prospective observational study of 200 consecutive patients with *P aeruginosa* bacteremia, mortality was significantly higher in patients given monotherapy (47%) than in patients given combination therapy (27%). It should be noted that the most common combination used was piperacillin or ticarcillin combined with tobramycin or gentamicin. The monotherapy group was dominated by patients given an aminoglycoside alone. Few patients received cephalosporins, aztreonam, carbapenems, or quinolones.\[^{27}\]

More recently, a prospective observational study from Israel evaluated monotherapy vs beta-lactam-aminoglycoside combination therapy for gram-negative bacteremia.\[^{28}\] Of the 2165 patients in the study, 16% had *P aeruginosa*. In this study, 34% (21 of 61) patients with *P aeruginosa* bacteremia died on beta-lactam monotherapy, whereas 28% (11 of 39) patients died after receipt of combination therapy. This corresponded to an odds ratio of 0.7 with 95% confidence intervals of 0.3-1.8.\[^{28}\] A meta-analysis of results from randomized controlled trials of antibiotic therapy for *P aeruginosa* did not show any benefit from combination therapy.\[^{29}\]

When combination therapy is used, a combination of antipseudomonal beta lactam plus aminoglycoside is typically given. Minimization of the aminoglycoside component of this regimen to 3-5 days may minimize the risk for toxicity.\[^{30}\] Combinations of beta lactams and quinolones are used increasingly often, but the clinical data to support such combinations are sparse. A randomized trial comparing ciprofloxacin plus piperacillin vs tobramycin plus piperacillin for empiric therapy in febrile neutropenic patients has been performed.\[^{31}\] However, just 4 of 543 febrile episodes were due to *P aeruginosa* bacteremia. Combinations of 2 beta lactams are not widely recommended. Double beta-lactam therapy has proved inferior to the beta-lactam plus aminoglycoside combination in animal models.\[^{32}\] A study in humans showed the emergence of resistance in 40% (2 of 5) of cases in a series of patients with *P aeruginosa* infection treated with double beta lactams.\[^{33}\]

Dosing of antimicrobial agents in therapy of serious *P aeruginosa* infections, such as ventilator-associated pneumonia or bacteremia, should be aggressive. For ciprofloxacin, an IV dose of 400 mg every 8 hours is recommended instead of standard 400 mg every 12 hours. Pharmacodynamically, levofloxacin 750 mg/day may be more effective than 500 mg/day for serious pseudomonal infections. Aminoglycosides, even when in combination therapy, should be dosed once daily when used against *P aeruginosa*. Aminoglycosides exhibit concentration-dependent bactericidal activity, and they produce prolonged postantibiotic effects. Tobramycin or gentamicin at 5-7 mg/kg/day and amikacin at 15-20 mg/kg/day are recommended for patients with normal renal function. For beta-lactam antibiotics, the time-dependent killing activity of the antibiotic class may be optimized by continuous IV infusion of the antibiotic. At this time, this approach remains to be validated in large clinical studies, but has little downside except for the need to dedicate an IV line for antibiotic administration. Carbapenems are not stable for a
full 24 hours, and prolonged (3-4 hour) infusions may be used as an alternative in order to optimize their time-dependent killing activity.

An unfortunate situation sometimes arises whereby *P. aeruginosa* isolates are resistant to all commercially available antibiotics except the polymyxins (colistin and polymyxin B). The polymyxins act primarily on the bacterial cell wall, leading to rapid permeability changes in the cytoplasmic membrane. Unfortunately, most pharmacokinetic studies on colistin were performed more than 30 years ago with intramuscular administration of the drug. Therefore, currently recommended doses of colistin may be suboptimal, and pharmacokinetic studies are urgently needed. A number of in vitro studies have suggested that use of colistin as part of combination therapy may result in greater killing of *P. aeruginosa* than monotherapy. Combinations have included colistin plus rifampin.\[^{34}\] This should be regarded as experimental, salvage therapy until robust clinical data become available.

**Acinetobacter Species**

*Acinetobacter* species may also be capable of virtually complete antibiotic resistance. As is the case with *P. aeruginosa*, resistance of *Acinetobacter* species may be mediated by a combination of beta lactamases and outer membrane protein deficiencies. The role of efflux pumps is largely unexplored in *Acinetobacter* species, but may be important. A clinically useful observation has been the in vitro efficacy of ampicillin-sulbactam in the face of resistance to almost all other drug classes. Sulbactam is able to bind to penicillin-binding protein 2 and therefore can impart direct antimicrobial activity against *Acinetobacter* species.\[^{35}\]

Carbapenems (for example, imipenem or meropenem) are often potent agents in the treatment of severe infections due to *Acinetobacter* species. This has been borne out in studies of *Acinetobacter* bacteremia.\[^{36}\] Ampicillin-sulbactam may represent a viable option to carbapenems.\[^{37}\] In patients with *Acinetobacter* strains that are resistant to virtually all currently available antibiotics, tigecycline or colistin may be the only viable option.\[^{38}\] As noted above, colistin has been combined with rifampin and other antibiotics, but reports of the success of these regimens are anecdotal only at this stage.

**Stenotrophomonas maltophilia**

*Stenotrophomonas maltophilia* is intrinsically resistant to carbapenems because of the production of carbapenem-hydrolyzing beta lactamases. *S. maltophilia* usually harbors 2 types of beta lactamase: L1, an MBL that hydrolyzes all beta lactams except aztreonam and is not inhibited by clavulanic acid, and L2, an inducible beta lactamase that hydrolyzes aztreonam but is inhibited by clavulanic acid. *S. maltophilia* strains harboring these beta lactamases hydrolyze almost all beta lactams and beta-lactam/beta-lactamase inhibitor combinations. However, the majority of strains are susceptible to ticarcillin-clavulanate, but not to ampicillin-sulbactam or piperacillin-tazobactam. *S. maltophilia* is frequently resistant to all aminoglycosides, probably due to impermeability of the outer membrane.
There are no randomized controlled trials that can guide therapy of *S. maltophilia*. TMP-SMX should be considered the primary therapeutic agent. Combination therapy is warranted in severe infections, such as bacteremia or pneumonia. However, it must be recognized that *S. maltophilia* may be a colonizer of the airways, in which case treatment is not needed. Appropriate antibiotics to use in combination with TMP-SMX include ticarcillin-clavulanate or ceftazidime.[39] Minocycline or tigecycline are active in vitro, but clinical data are sparse. Quinolones should be avoided as monotherapy for *S. maltophilia*.

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<th>6. When should combination therapy be used for treatment of infections with <em>P. aeruginosa</em>?</th>
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<tr>
<td>☑️ Almost always</td>
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<td>☐️ Sometimes</td>
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<tr>
<td>☐️ Rarely</td>
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<td>☐️ Almost never</td>
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**Explanation:**
"Almost always" is the best answer because this pathogen is often resistant to 1 or more of the antipseudomonal antibiotics, but "Usually" is also reasonable.

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### Empiric Antibiotic Selection

Appropriate empiric antibiotic selections can be made if the likely pathogens (and their susceptibility profiles) at any particular infection site are known. Cumulative antibiotic susceptibility reports on multiple patients (antibiograms) or national susceptibility data can be useful in guiding empiric antibiotic therapy. Additionally, empiric antibiotic selection should be individualized by taking into account recent antibiotic use and known bacterial colonization status. For example, specific antibiotics should not be used if they have been administered to the patient. Additionally, if a patient is known to have been colonized with highly resistant organisms, the antibiotic choice should be modified to reflect this.
Ventilator-Associated Pneumonia

Guidelines for empiric therapy for ventilator-associated pneumonia have been published by the American Thoracic Society and the Infectious Diseases Society of America. The key requirements for empiric antibiotic therapy for late-onset ventilator-associated pneumonia are that multiresistant *P. aeruginosa* and MRSA should be covered. Therefore, empiric treatment for multiresistant *P. aeruginosa* should consist of the combination of an antipseudomonal beta lactam plus either an aminoglycoside or an antipseudomonal quinolone. Empiric treatment for MRSA should consist of vancomycin or linezolid; daptomycin is not appropriate therapy for pneumonia, and results of trials of tigecycline for nosocomial pneumonia are not yet available.

These guidelines seem appropriate in most circumstances. In some ICUs, there may be a need to empirically cover carbapenem-resistant *Acinetobacter* species. High rates of resistance to colistin have been observed when colistin is used empirically. Tigecycline may be an appropriate choice in this setting because the drug may cover multiply resistant *Acinetobacter* species plus MRSA; however, tigecycline will not cover *P. aeruginosa*.

Intra-abdominal Infections

Guidelines for empiric therapy for intra-abdominal infections have been published by the Infectious Diseases Society of America, the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Diseases Pharmacists. These guidelines list, as recommended agents for high-severity infections, piperacillin-tazobactam, imipenem, meropenem, third/fourth-generation cephalosporins plus metronidazole, ciprofloxacin plus metronidazole, and aztreonam plus metronidazole. Since the time when this guideline was published, tigecycline has been approved for treatment of intra-abdominal infections.

Skin and Soft-Tissue Infections

The Infectious Diseases Society of America has published guidelines for the treatment of skin and soft-tissue infections. Most of these serious infections in hospitalized patients will be due to MRSA. Options listed for management of suspected MRSA skin and soft-tissue infections include vancomycin, linezolid, clindamycin, daptomycin, doxycycline, minocycline, and TMP-SMX. As noted above, since the time when this guideline was published, tigecycline has been approved for the treatment of skin and soft-tissue infections.
7. Which of the following antibiotic regimens would not be appropriate for a patient hospitalized with serious intra-abdominal infections?

- Cefepime
- Ciprofloxacin plus metronidazole
- Imipenem
- Piperacillin-tazobactam
- Tigecycline

**Explanation:**
Cefepime without an antianaerobic agent, such as metronidazole, would not generally be recommended for these polymicrobial infections.

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**Self-Assessment Case 1: Nosocomial Postappendectomy Secondary Peritonitis**

LP is a 30-year-old woman who underwent laparoscopic appendectomy for perforated appendix 2 weeks ago. Cefazolin was used as prophylaxis. She is referred to your practice 6 days after discharge from the hospital with vague abdominal pain, fever mostly in the evening, night sweats, anorexia, and weight loss. Physical examination reveals febrile, tachycardic patient with abdominal tenderness and lack of bowel sound. Clinical work-up results confirmed peritonitis and abscesses, which were drained percutaneously.

**Case 1, question 1:**

8. Which would be your approach to empiric antibiotic therapy in this patient?

- Initiate broad-spectrum antibiotic and narrow when culture results are available

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<th>Initiate narrow-spectrum antibiotic and add antibiotics when culture results are available</th>
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<td>Wait for 24 hours for culture results</td>
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<td>Repeat cefazolin</td>
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**Self-Assessment Case 1 (Continued)**

Peritoneal fluid culture result was positive for *E. cloacae* resistant to multiple antibiotics, including both ceftazidime and imipenem.

**Case 1, question 2:**

9. Which one of the following would you choose as continuation of your management in this case?

- Ertapenem
- Tigecycline
- Ceftriaxone
- Linezolid

**Self-Assessment Case 2: Ventilator-Associated Pneumonia With MRSA: Empiric Therapy in General and Empiric Therapy Based on Organism**

KO is a 32-year-old man who was admitted to the hospital 15 days ago following a motor vehicle accident that resulted in significant head trauma, flail chest, and a severely
contaminated wound of his right leg. Oxacillin monotherapy was initiated on admission. This treatment was changed to vancomycin 2 days later when wound culture results revealed MRSA sensitive to vancomycin, which was administered for 7 days.

KO has been on a ventilator since admission, and has yet to regain consciousness. *P aeruginosa* has not been a significant problem in this ICU. His temperature, which was previously normal, recorded 38.8°C in the evening. Furthermore, his oxygen saturation dropped below 90% on 30% inhaled oxygen and chest x-ray revealed new infiltrate. Blind bronchial suction samples revealed thickened secretions with many white blood cells, scattered gram-negative bacilli, and numerous gram-positive cocci in gram stain. Blood sample and bronchial secretion were sent for culture and sensitivity tests. No other site for infection was found. You decide to begin empiric antibiotic therapy for KO's ventilator-associated pneumonia.

**Case 2, question 1:**

10. Which one of the following would you consider for empiric antibiotic therapy in this patient?

- [ ] Vancomycin
- [ ] Linezolid + levofloxacin
- [ ] Daptomycin + levofloxacin
- [ ] Daptomycin + aztreonam

**Self-Assessment Case 2 (Continued)**

Thirty-six hours later, culture result was reported positive for *Acinetobacter* species, but no sensitivity result is available yet.

**Case 2, question 2:**
11. Which of the following would be your concern with treating *Acinetobacter* species?

- [ ] No randomized controlled trials to guide therapy
- [ ] May be capable of virtually complete antibiotic resistance
- [ ] Treatment will not be successful when susceptibility is unknown
- [ ] None of the above would be a concern

**Summary**

In summary, the prevalence of antibiotic resistance in both gram-positive and gram-negative nosocomial pathogens is high and increasing. However, there is great variation between countries, hospitals, and even individual ICUs within a single hospital. The hospital or unit antibiogram (that is, the cumulative antibiotic susceptibility report) and national surveillance data are key guides to the selection of antibiotics for empiric antimicrobial therapy. Antibiotic choice must be individualized, and patients with serious or life-threatening infections should receive initial broad-spectrum therapy that is subsequently narrowed when pathogen identity and susceptibility results become available allowing pathogen-directed therapy. Resistance mechanisms vary among different pathogens, but multidrug resistance is a substantial problem in *S. aureus, K pneumoniae, Enterobacter* species, *P. aeruginosa*, and *Acinetobacter* species as well as other less commonly encountered pathogens.

Antibiotic selection differs for gram-positive and gram-negative pathogens. Several new agents (linezolid, daptomycin, and tigecycline) are available to supplement vancomycin for treatment of MRSA and VRE. Enterobactereaceae that produce ESBLs (especially *Klebsiella* species), AmpC beta lactamases (especially *Enterobacter* species), or KPC or MBL carbapenemases may be resistant to all beta-lactam antibiotics as well as most other antibiotic classes. *P. aeruginosa* has multiple resistance mechanisms, usually requires combination therapy with antipseudomonal antibiotics, and are sometimes resistant to all antibiotics except polymyxins. *Acinetobacter* species are often treated with carbapenems,
and colistin or tigecycline may be the only viable option for carbapenem-resistant *Acinetobacter* species.

Recently published treatment guidelines in regard to empiric antibiotic selection for common serious infections, such as ventilator-associated pneumonia, intra-abdominal infections, and skin and soft-tissue infections, do not include the newest antimicrobial agent tigecycline, which is active in vitro against both MRSA and many gram-negative pathogens, including *Acinetobacter* species, but not *P. aeruginosa*.

Maximizing therapeutic success in an era of increasing antibiotic drug resistance requires careful use of all the available antibiotic options that are based on the best information available about the pathogens infecting the patient being treated.

*Supported by an independent educational grant from Wyeth.*

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**12.** Which of the following properties distinguishes an ESBL from an AmpC beta lactamase?

- Inhibition by clavulanic acid
- Activity against carbapenems, such as imipenem
- Activity against third-generation cephalosporins, such as ceftazidime
- Association with resistance to multiple types of beta-lactam antibiotics
- Association with resistance to multiple, different classes of antibiotics

**Explanation:**
"Inhibition by clavulanic acid" is the only property listed that distinguishes the 2 types of beta lactamases.

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**References**


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