The therapy of severe pneumonia can be used as a paradigm to demonstrate the principles of antibiotic therapy of critically ill patients. The focus of this discussion will be on empiric antibiotic therapy, but the principles of antibiotic penetration and concentration in the lung are summarized in Table 1.

**Mechanisms of Action**

Antibiotics interfere with the growth of bacteria by undermining the integrity of their cell wall or by interfering with bacterial protein synthesis or common metabolic pathways. The terms *bactericidal* and *bacteriostatic* are broad categorizations, and may not apply for a given agent against all organisms, with certain antimicrobials being bactericidal for one bacterial pathogen, but bacteriostatic for another. Bactericidal antibiotics kill bacteria, generally by inhibiting cell wall synthesis or by interrupting a key metabolic function of the organism. They include the penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, rifampin, and metronidazole. Bacteriostatic agents inhibit bacterial growth, do not interfere with cell wall synthesis, and rely on host defenses to eliminate bacteria. They include the macrolides, tetracyclines, sulfa drugs, chloramphenicol, and clindamycin. The distinction between these two types of agents may not be important in the therapy of lung infections, as either can be effective. When neutropenia is present, or if there is accompanying endocarditis, meningitis, or osteomyelitis, then the use of a bactericidal agent may be advantageous.

Antimicrobial activity is often described by the terms *minimal inhibitory concentration* (MIC) and *minimal bactericidal concentration* (MBC). The term MIC defines the minimum concentration of an antibiotic that inhibits the growth of 90% of a standard-sized inoculum, leading to no visible growth in a broth culture. The term MBC refers to the minimum concentration needed to cause a 3-log drop (99.9% killing) in the size of the standard inoculum. These terms must be interpreted cautiously and, if pneumonia is the infection being treated, the clinician must consider MIC and MBC data with a knowledge of how well an agent can reach the lung. The MIC is used to define the “sensitivity” of a pathogen to a specific antibiotic, under the assumption that the concentration required for killing can be reached *in vivo*, but lung concentrations may be substantially lower than serum concentrations, the latter being the site that is generally used to define antimicrobial susceptibility patterns.

**Penetration Issues**

The concentration of an antibiotic in the lung depends on the permeability of the capillary bed at the site of infection (the bronchial circulation), the degree of protein binding of the drug, and the presence or absence of an active transport site for the antibiotic in the lung. In the lung, the relevant site to consider for antibiotic penetration is controversial and not clearly defined. Sputum and bronchial concentrations are considered most relevant for bronchial infections, while concentrations in lung parenchyma, epithelial lining fluid, and in cells such as macrophages and neutrophils are probably more important for pneumonic infections. The localization of the pathogen may also be important, and intracellular organisms such as *Legionella pneumophila* and *Chlamydia pneumoniae* are probably best eradicated by agents that achieve

---

**Table 1. Penetration of Antibiotics Into Respiratory Secretions**

<table>
<thead>
<tr>
<th>Lipid-Soluble, Concentrate Independent of Inflammation, Good Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolones</td>
</tr>
<tr>
<td>New macrolides: azithromycin, clarithromycin</td>
</tr>
<tr>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relatively Lipid-Insoluble, Inflammation-Dependent for Concentration in the Lung, Poor Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Beta-lactams</td>
</tr>
<tr>
<td>Penicillins</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Monobactams</td>
</tr>
<tr>
<td>Carbapenems</td>
</tr>
</tbody>
</table>
high concentrations in macrophages. Although local concentration of an antibiotic is important, it is also necessary to consider the activity of an agent at the site that it reaches. For example, antibiotics can be inactivated by certain local conditions. Aminoglycosides have reduced activity at acidic pH levels, and some pneumonic areas of lung are acidic. Bacteria can produce beta-lactamase enzymes that can render a number of common penicillins and cephalosporins inactive. In addition, bacteria can become resistant to an agent (requiring that higher concentrations than are possible to achieve be present in order to be killed) because they become impermeable to antibiotic entry or because they modify the site to which the antibiotic must bind in order to be active.

**Specific Antibiotics**

**Beta-Lactam Antibiotics**

These bactericidal antibiotics have in common the presence of a beta-lactam ring, which is bound to a five-membered thiazolidine ring in the case of the penicillins and to a six-membered dihydrothiazine ring in the case of the cephalosporins. Modifications in the thiazolidine ring can lead to agents such as the penems (imipenem and meropenem), while absence of the second ring structure characterizes the monobactams (aztreonam). These agents can also be combined with beta-lactamase inhibitors such as sulbactam, tazobactam, or clavulanic acid, to create the beta-lactam / beta-lactamase inhibitor drugs. These agents extend the antimicrobial spectrum of the beta-lactams by providing a substrate for the bacterial beta-lactamases (sulbactam, clavulanic acid, tazobactam), thereby preserving the antibacterial activity of the parent compound. Beta-lactam antibiotics work by interfering with the synthesis of bacterial cell wall peptidoglycans by binding to bacterial penicillin binding proteins.

The penicillins used for respiratory tract infections include the natural penicillins (penicillin G and V), the aminopenicillins (ampicillin, amoxicillin), the antistaphylococcal agents, the antipseudomonal agents, and the beta-lactam / beta-lactamase inhibitor combinations. The antipseudomonal penicillins include the older carboxypenicillins (ticarcillin) and the ureidopenicillins (piperacillin, azlocillin, mezlocillin), with piperacillin and azlocillin being the most active agents against *Pseudomonas aeruginosa*. The beta-lactamase inhibitor combinations include clavulanic acid with either amoxicillin or ticarcillin; sulbactam with ampicillin; and tazobactam with piperacillin.

The cephalosporins span from first to fourth generation. The earlier agents were generally active against Gram-positive organisms, but did not have extended activity to the more complex Gram-negative organisms or anaerobes, and were susceptible to destruction by bacterial beta-lactamases. The newer-generation agents are generally more specialized agents with broad-spectrum activity and with more mechanisms to resist breakdown by bacteria. The second-generation and newer agents are resistant to bacterial beta-lactamases. The third-generation agents active against penicillin-resistant pneumococci include ceftriaxone and ceftazidime, while ceftazidime is active against *P. aeruginosa*. The third-generation agents, as mentioned above, may induce beta-lactamases among certain Gram-negative organisms, and thus promote the emergence of resistance during monotherapy. The fourth-generation agent, cefepime, is active against pneumococci and *P. aeruginosa*, but is also less likely to induce resistance among the Enterobacteriaceae than the third-generation agents.

Imipenem and meropenem are the broadest-spectrum agents in this class, being active against Gram-positive organisms, anaerobes, and Gram-negative organisms including *P. aeruginosa*. They have shown efficacy for patients with severe pneumonia, both community-acquired and nosocomial, and may be effective as monotherapy, taking into account the caveats discussed above. Aztreonam is a monobactam that is so antigenically different from the rest of the beta-lactams that it can be used in penicillin-allergic patients. It is active only against Gram-negative organisms, having a spectrum very similar to the aminoglycosides.

**Fluoroquinolones**

These bactericidal agents act by interfering with bacterial DNA gyrase, leading to impaired DNA synthesis, repair, transcription, and other cellular processes, resulting in bacterial cell lysis. DNA gyrase is one form of bacterial topoisomerase enzyme that is inhibited by the quinolones, but activity against other similar enzymes is part of the effect of a variety of quinolones. Quinolones kill in a concentration-dependent fashion, related to the peak serum concentration / MIC ratio and to the area
under the curve/MIC ratio of drug concentration relative to organism susceptibility.

There are two features of quinolones that make them well-suited to respiratory infections. First, they penetrate well into secretions and inflammatory cells within the lung, achieving concentrations that exceed serum levels in many instances. Thus, these agents may be clinically more effective than predicted by MIC values. Secondly, these agents are highly bioavailable with oral administration, and thus similar levels can be reached if administered orally or IV. This allows for some “borderline” patients (such as nursing-home patients) with pneumonia to be managed with outpatient oral therapy and not be admitted solely for the purpose of IV therapy to achieve high serum levels of antibiotics. In addition, the high bioavailability of these agents permits an easy transition from IV to oral therapy of inpatients with pneumonia, facilitating early discharge when the patient is doing well, and permitting ongoing oral therapy with maintenance of high serum levels of antibiotics.

Currently, the quinolones fall into several “generations.” The first-generation agents had Gram-negative activity only and were used for urinary tract infections, epitomized by the agent nalidixic acid. The second-generation agents had added Gram-positive activity and could be used for systemic infections; they included ciprofloxacin, ofloxacin, pefloxacin, fleroxacin, and lomefloxacin. These agents had limited value for respiratory infections because of relatively high MIC values among pneumococci, making it necessary to use high doses to achieve efficacy against this pathogen. The third-generation agents are characterized by better Gram-positive activity, particularly against pneumococcus. These agents include levofloxacin, gatifloxacin, and moxifloxacin, which are currently available. Among the third-generation agents, the most active against pneumococcus is moxifloxacin, followed by gatifloxacin and then levofloxacin. These new agents also have long half-lives, allowing once-daily dosing with most of the third-generation agents. In addition, quinolones that are active against pneumococcus are likely to be effective regardless of penicillin susceptibility patterns because penicillin and quinolone resistance do not generally occur together in the same organisms, and pneumococcal resistance rates to new quinolones are low. However, some coexistence of quinolone resistance with penicillin resistance has been re-

ported, and the most active pneumococcal agents (on an MIC basis) are the least likely to develop resistance. With this in mind, it is not surprising that there have been reports of failures of therapy for pneumococcal community-acquired pneumonia (CAP) using levofloxacin. When quinolones are used for severe CAP, the current recommendation is not to use them as monotherapy.

**Aminoglycosides**

These bactericidal agents act by binding to the 30S ribosomal subunit of bacteria, thus interfering with protein synthesis. Aminoglycosides have primarily a Gram-negative spectrum of activity and are usually used in combination with other agents targeting difficult organisms such as *P. aeruginosa* or other resistant Gram-negative organisms. When combined with certain beta-lactam agents, they can achieve antibacterial synergy against *P. aeruginosa*. Amikacin is the least susceptible to enzymatic inactivation by bacteria, while tobramycin is more active than gentamicin against *P. aeruginosa*. Aminoglycosides penetrate poorly into lung tissue, and can be inactivated by the acid pH levels that are common in pneumonic lung tissue. Thus, in one clinical trial of nosocomial pneumonia therapy, the use of an aminoglycoside with a beta-lactam was no more effective than a beta-lactam alone, and the combination regimen was not more effective in preventing the emergence of pseudomonal resistance during therapy than was the monotherapy regimen with a beta-lactam. In the treatment of bacteremic pseudomonal pneumonia, aminoglycoside combination therapy may be more effective than monotherapy.

Aminoglycosides kill in a concentration-dependent fashion, and can be given once daily to optimize killing while attempting to minimize toxicity. In clinical practice, this has not been proven to occur, and once-daily dosing is comparable in efficacy and nephrotoxicity to regimens using multiple daily doses. When aminoglycosides are used, it is necessary to monitor serum levels to minimize the occurrence of acute renal failure. Peak concentrations correlate with efficacy, but have meaning only with multiple daily doses, and their utility in once-daily regimens has not been established. Trough concentrations are monitored to minimize toxicity and probably should be followed regardless of dosing regimen.
Because of poor penetration into tissues, some investigators have used nebulized aminoglycosides for the therapy and/or prevention of Gram-negative pneumonia. This approach has been effective in the treatment of infectious exacerbations of cystic fibrosis, but has not been effective as adjunctive therapy to systemic antibiotics in patients with serious respiratory tract infections.

**Oxazolidinones (Linezolid)**

Linezolid is the first agent in a new class of antibiotics, the oxazolidinones, which act to inhibit bacterial protein synthesis. They work by binding to the 50S ribosomal subunit and preventing the binding of transfer RNA and preventing the formation of the 70S initiation complex. This is a unique mechanism and no cross-resistance to other agents is likely.

Linezolid is active against methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (VRE) [both *Enterococcus faecium* and *Enterococcus faecalis*]. It is bacteriostatic, but bactericidal against some pneumococci. The kinetics suggest that the drug will be active at an MIC of ≤ 4 mg/L, and MRSA, penicillin-resistant *S pneumoniae*, and VRE all fall in this range. Dosing is 600 mg twice daily. The agent has high bioavailability, and thus serum levels are the same with oral or IV therapy. The half life is 4.5 to 5.5 h. Peak concentration is 18 mg/L after a 600-mg dose. Renal and nonrenal clearance occur, and dosing adjustment is not needed for patients with renal failure.

Efficacy has been shown for nosocomial pneumonia, CAP, complicated skin/soft tissue infections, and VRE. One recent analysis suggests that linezolid may be superior to vancomycin for the therapy of ventilator-associated pneumonia (VAP) caused by MRSA.

Side effects are not common and the agent is well tolerated. Nausea, diarrhea, anemia, and thrombocytopenia (with prolonged use, < 1%) can occur. It is also a weak monoamine oxidase inhibitor.

**Using Proper Dosing and Dosing Regimens**

When an antimicrobial agent is used appropriately, it must be dosed in a manner that takes into account several factors, including its mechanism of action, its activity relative to the MIC of the target organism, and its penetration to the site of infection. Bactericidal antibiotics can kill bacteria in a time-dependent or concentration-dependent fashion. Time-dependent killing means that the organism is eradicated only as long as the concentration of antibiotic stays above the MIC of the target organism. The minimal time needed to exceed the MIC of the infecting pathogen is unknown, but most estimates are for at least 40% of the dosing interval. Drugs that kill in a concentration-dependent fashion are the beta-lactams (penicillins and cephalosporins) and vancomycin. When time-dependent killing has been studied, the antibiotic concentration used to define the effect is the serum level, and this measurement may not account for the penetration of antibiotics to the site of infection. For example, some agents (quinolones, macrolides, and the oxazolidinone linezolid) penetrate well into sites of infection such as the lung, achieving levels in lung tissue that exceed the serum level, while other agents (penicillins, cephalosporins, vancomycin) penetrate poorly, achieving levels in lung tissue below serum concentrations. Thus, for some drugs, serum concentrations may not accurately reflect time above MIC at the site of infection. In theory, with an antibiotic that kills in a time-dependent fashion, optimal killing, with minimal total dose of antibiotic, could be achieved by continuous infusion administration, but this approach has not been shown to have any beneficial effect on clinical success in the therapy of nosocomial pneumonia in trauma patients when ceftazidime has been administered in this fashion.

Antibiotics that kill in a concentration-dependent fashion are best administered as once-daily doses. This approach achieves high peak concentrations in the serum, thus maximizing efficacy, but with low trough concentrations, which may minimize the toxicity of agents such as the aminoglycosides. For some agents, the concept of once-daily dosing not only takes advantage of concentration-dependent killing, but also relies on the postantibiotic effect of agents, meaning that they continue to kill even after the serum concentration falls below the MIC. Aminoglycosides have a good postantibiotic effect against enteric Gram-negative organisms, and thus have been used with once-daily dosing regimens without any significant impact on efficacy or toxicity. When concentra-
tion-dependent killing is present, the effect of the agent on the bacteria can be defined by examining the peak serum concentration relative to the MIC, or by looking at the area under the concentration time curve, divided by the MIC (the AUIC). For pneumococcus, quinolone killing is optimized by a peak serum concentration:MIC ratio of 12:1, or an AUIC of ≥ 30. For resistant Gram-negative organisms, the optimal AUIC for quinolones may be as high as 110 to 125.

Streamlining Antimicrobial Therapy

As the importance of using broad-spectrum regimens when initiating empiric therapy has been stressed, it is equally important for clinicians to narrow or discontinue therapy when more data on the patient’s clinical progress and the microbiologic data become available. In the ICU, combination therapy may be needed for certain resistant pathogens such as *P. aeruginosa* or mixed infections involving resistant Gram-positive and Gram-negative organisms. Once the clinical response has been observed and culture data are available, the patient’s therapy can often be switched to fewer antibiotics, targeted to the cultures. Singh has shown that the duration of therapy can also be reduced in many patients based on clinical evaluation of signs and symptoms. One recent study documented that the use of a broad-spectrum empiric regimen for suspected VAP could be coupled with the intentional discontinuation of therapy after 7 days if further therapy was not absolutely necessary. With this protocol, the duration of antibiotic therapy was reduced with no significant impact on mortality, but a significant reduction in the incidence of respiratory superinfections.

Empiric Therapy of Pneumonia: an Example of Antibiotic Usage

If the source of infection is unknown, or if it is known to be intra-abdominal, empiric therapy can be given as in Table 2. Patients with severe pneumonia can be divided into three different categories, each with its own list of likely pathogens, and from this list follow suggested antibiotic regimens. In order to decide which category a patient falls into, it is first necessary to determine if the pneumonia is community-acquired or hospital-acquired. Patients with severe CAP are likely to be infected with pneumococcus, Legionella, other atypical organisms, *S. aureus*, and enteric Gram-negative organisms; they should receive the therapy directed to these pathogens. In the setting of severe hospital-acquired pneumonia (HAP), stratification is identical whether the patient is intubated or not, but patients are separated on the basis of whether or not they have risk factors for resistant pathogens. If no risk factors are present and if the pneumonia is early-onset (within the first 4 days of admission), then the patient is at risk for nonresistant Gram-negative organisms and *S. aureus*, pneumococcus, and *Haemophilus influenzae*, and should receive therapy for these organisms. If the patient has late-onset HAP (day 5 or later) in the absence of risk factors, or pneumonia of any time of onset in the presence of risk factors, then the patient should be treated for potentially resistant Gram-positive and Gram-negative organisms.

Although all patients undergo some diagnostic testing, empiric antibiotic therapy must be initiated before the results of diagnostic testing become available. Empiric therapy is needed for CAP patients for several reasons: (1) Even with extensive diagnostic testing, no diagnosis is found in up to half of all patients; (2) the bacteriology of severe CAP is predictable, making empiric therapy possible; and (3) in the setting of severe CAP, accurate empiric therapy has been shown to improve outcome. Similarly, empiric therapy, based on a clinical diagnosis of infection, is necessary for patients with severe HAP because (1) clinical criteria are sensitive to early and potentially treatable forms of pneumonia; (2) algorithms can be used to predict the likely pathogens and to guide therapy; and (3) empiric therapy can be modified once the results of tracheal aspirates or sputum cultures become available.

Table 2. Empiric Therapy of Sepsis

<table>
<thead>
<tr>
<th>Source Unknown</th>
<th>Organisms: <em>S. aureus</em> (especially if IV line), Gram-negative organisms, fungi (steroids, prior antibiotics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy:</td>
<td>Dual pseudomonal +/– oxacillin, vancomycin or alternatives</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intra-abdominal Source</th>
<th>Organisms: Gram-negative organisms, anaerobes, enterococci (latter two more with secondary vs primary infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy:</td>
<td>Ceftriaxone, ertapenem, ampicillin/sublactam, +/– clindamycin/metronidazole or imipenem, meropenem, piperacillin/tazobactam +/– vancomycin, linezolid</td>
</tr>
</tbody>
</table>
Severe CAP

Because the spectrum of likely pathogens is so broad and includes not only pneumococcus but also Legionella spp and enteric Gram-negative organisms, it is necessary to use multiple IV agents. This includes an IV macrolide or quinolone with the addition of other agents, the type and number being determined by whether risk factors for P aeruginosa are present.

The initial empiric regimen for severe CAP should be adequate for a penicillin-resistant pneumococcal infection. Recent studies have shown that most resistance is of the intermediate, and not high-level type. As many as 85 to 90% of penicillin-resistant organisms are still macrolide-sensitive, and high-dose beta-lactam therapy, with a penicillin or third-generation cephalosporin, is also adequate for most resistant pneumococci. If penicillin resistance is especially likely, then cefotaxime or ceftiraxone should be used instead of an antipseudomonal third-generation cephalosporin. If a resistant pneumococcal infection is suspected and cultures of blood or sputum show high-level resistance to both cephalosporins and penicillin, then therapy should include either vancomycin or a new antipseudomococcal quinolone.

One organism that is not well covered by the suggested empiric regimens is S aureus. This organism is not a common cause of severe CAP, but it is a concern when patients have diabetes mellitus or renal failure or after influenza infection. In these settings, the use of an antistaphylococcal penicillin or vancomycin should be considered, possibly in place of one of the antipseudomonal agents.

Severe HAP

Patients with no risk factors for resistant pathogens and early onset of HAP are at risk for only the core pathogens, and they can often be treated with only a single antimicrobial agent. However, when patients are at risk for P aeruginosa or other resistant pathogens—because of the presence of risk factors such as prior antibiotics, corticosteroid use, or malnutrition, or because of prolonged mechanical ventilation (≥ 5 days) leading to late-onset pneumonia—combination therapy is necessary. Combination antipseudomonal therapy should be started in these patients, and continued if P aeruginosa or other resistant Gram-negative organisms (such as Enterobacter spp) are present. In immune-compromised patients, combination therapy can provide synergism against P aeruginosa, but this is not the usual reason for using combination regimens in other types of patients. The rationale for combination therapy is to prevent the emergence of resistance during treatment, a common event when only a single antimicrobial agent is used for these pathogens. In addition, there is evidence that dual-agent therapy can improve the outcome of patients with bacteremic P aeruginosa pneumonia.

The antimicrobials that are antipseudomonal (Table 3) are either beta-lactams (penicillins, cephalosporins, monobactams, and carbapenems) or agents from other drug classes. These include penicillins such as piperacillin and mezlocillin; the beta-lactam/beta-lactamase inhibitor combination ticarcillin/clavulanate; the third-generation cephalosporins, ceftazidime and cefepime; the monobactam, aztreonam; the carbapenem, imipenem; a fluoroquinolone, ciprofloxacin; and the aminoglycosides. When these agents are combined, three general approaches can be used. The traditional combination includes a beta-lactam and an aminoglycoside, which can achieve antibacterial synergy. This is rarely an important benefit for the nonneutropenic patient and it requires the use of an aminoglycoside, which has several limitations in the critically ill pneumonia patient. Aminoglycosides should be administered once daily, to take advantage of their enhanced killing when high peak levels are achieved, but even with this type of regimen, nephrotoxicity can occur. In addition, aminoglycosides penetrate poorly into the lung and may not be active at the acid pH levels that are common in pneumonic lung tissue.

Recently, Hatala and associates conducted a meta-analysis of once-daily aminoglycoside dosing studies and concluded that, compared with standard dosing regimens, bacteriologic cure rates are

<table>
<thead>
<tr>
<th>Table 3. Antipseudomonal Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quinolones:</strong> ciprofloxacin</td>
</tr>
<tr>
<td><strong>Aminoglycosides:</strong> gentamicin, amikacin, tobramycin</td>
</tr>
<tr>
<td><strong>Beta-lactams</strong></td>
</tr>
<tr>
<td>Antipseudomonal penicillins</td>
</tr>
<tr>
<td>Cephalosporins: ceftazidime, cefepime</td>
</tr>
<tr>
<td>Imipenem, meropenem</td>
</tr>
<tr>
<td>Aztreonam</td>
</tr>
<tr>
<td>Beta-lactam/beta-lactamase inhibitor combinations: piperacillin/tazobactam, ticarcillin/clavulanate</td>
</tr>
</tbody>
</table>
identical, but once-daily dosing regimens may have reduced toxicity. Given the ease of using these agents in a single daily dose and the associated reduced costs of this approach, the findings in this analysis may be sufficient to justify the widespread use of such dosing regimens.

An alternative type of combination regimen is to use two beta-lactam agents, but this approach can lead to antagonism in the mechanism of action of the two drugs, and if one drug induces a bacterial beta-lactamase, both drugs may be simultaneously inactivated. A third type of combination is to use ciprofloxacin with a beta-lactam, thus avoiding a dual beta-lactam regimen and avoiding the use of an aminoglycoside. This regimen also has the advantage of excellent respiratory tract penetration by the quinolone agent, ciprofloxacin.

In some patients with severe HAP, additional empiric therapy with vancomycin may be needed for possible MRSA infection, another organism seen in patients with late-onset pneumonia after prolonged intubation or prior antibiotic therapy. In the intubated patient, tracheal aspirates can be used to identify the pathogen(s) present, and therapy can be reduced to a single agent if *P. aeruginosa*, other resistant Gram-negative organisms, and MRSA are not present. One recent multicenter trial showed that when such organisms were absent, patients with severe HAP could be successfully treated with a single agent such as ciprofloxacin or imipenem.

### Antibiotic Resistance

There are four basic mechanisms of resistance:

1. Decreased permeability of microbial cell wall. This is an important mechanism for Gram-negative resistance and is caused by alteration of porin channels.
2. Production of destructive enzymes, such as beta-lactamases. This is the major mechanism for Gram-negative resistance and can combine with altered permeability in specific organisms. Beta-lactamases can be type I or extended spectrum, and are commonly produced by organisms like *P. aeruginosa* and the Enterobacteriaceae. Resistance to third-generation cephalosporins is often mediated by this mechanism.
3. Alteration of the target site of action, such as the penicillin-binding proteins, the DNA gyrase (quinolones), and RNA polymerase. This is an important mechanism for Gram-positive resistance.
4. Active efflux of the antibiotic, which can occur in Gram-positive and Gram-negative organisms, but is an important mechanism of macrolide resistance in pneumococci.

### Antimicrobial Control Programs

Antimicrobial control programs, such as guidelines, standards, prior authorization policies, and performance measures, primarily focus on limiting antibiotic use. Several studies evaluating antibiotic control programs have not demonstrated reduced resistance rates. This may relate to the fact that other variables besides antibiotic use in ICUs determine the presence of resistance in the hospital. The type of antimicrobial control program that is used in a given hospital may be best dictated by a knowledge of local antibiotic usage and resistance patterns. If, for example, antibiotic usage is controlled and appropriate, and a single strain of a highly-resistant pathogen is present, then there may be a need for more intensive infection-control efforts. If, on the other hand, usage is high and inappropriate, and many strains of resistant pathogens are prevalent, control of antibiotic usage may be the most pressing need.

### Annotated References


Classic article showing that third-generation cephalosporins can promote the emergence of resistance during therapy of Enterobacter bacteremia, and also a risk factor for resistance that is present prior to therapy.


Addition of an aminoglycoside to imipenem for the therapy of nosocomial pneumonia was not associated with improved outcomes, but only with a higher rate of nephrotoxicity.

Craig W. Pharmacodynamics of antimicrobial agents
Multicenter randomized trial comparing ciprofloxacin 400 mg q8h to imipenem 1 g q8h and showing both to be effective monotherapy for severe VAP, provided no highly resistant organisms were present.

Landmark study showing that outcome in nosocomial pneumonia is improved if the AUIC of the drug used is ≥ 125, especially for Gram-negative infections.


Study showing a mortality benefit for combination therapy vs monotherapy in patients with bacteremic P aeruginosa pneumonia.

Study that documents the need to achieve a peak concentration: MIC ratio of 10 to 12 to optimize outcomes in the therapy of CAP due to pneumococcus.

Notes