Antibiotic resistance, a growing concern worldwide, can occur with any organism but actually involves relatively few species. It is not an inevitable consequence of antibiotic use, and it is a popular misconception that resistance necessarily follows indiscriminate or prolonged antibiotic usage. Resistance may be natural or acquired.

Acquired antimicrobial resistance may result from the clonal spread of a resistant organism or from use of the agent. The clonal spread of resistant strains results from a breakdown of infection-control measures that fail to limit the strain to a confined geographical area. Antibiotic resistance that is associated with antibiotic use is not related to a single strain, as in clonal spread of resistant strains results from a breakdown of control measures. On a national level, antibiotics should be eliminated from animal feeds and animal products, which can find their way into human populations when people consume meat and poultry.

This series on antibiotics emphasizes factors that hospital formulary committees and practitioners should consider when selecting antimicrobials. The resistance potential of an antibiotic is one such underappreciated factor. By selectively choosing antibiotics rather than selectively using them, we have the best chance of prolonging the useful life of an antimicrobial armamentarium.1–4

**MECHANISMS OF RESISTANCE**

The precise mechanism of antibiotic resistance is not entirely understood. Antibiotics are known to induce genetic mutations in bacteria. Changes in bacterial DNA may be chromosomal or plasma-mediated. Chromosomal mutations are less common and involve a stable change in the genetic makeup of bacteria and are, in the main, limited to one species.

Plasma-mediated resistance may be spread from species to species and may be expressed or repressed. As the most common type of resistance, it is potentially the most damaging, because plasmids transmit resistance genes not only from one bacterium to another but also from one species to another. Although the precise mechanism is not always apparent, several lessons have become clear during the past several decades.

First, some antibiotics are more likely than others to induce resistant genes in bacteria. If an antibiotic does induce a change in resistance, it usually does so within two years after the antibiotic’s release for general use. Antibiotics that tend not to induce changes in resistance continue relatively resistance-free for decades. Antibiotics that develop resistance within the first two years after general use continue to induce resistance for the duration of the drug’s existence.

Second, resistance to an antibiotic occurs with one or two microorganisms, but antibiotic activity is preserved against other organisms in the antibiotic’s usual spectrum of activity.

**RESISTANCE POTENTIAL**

The best way to control antibiotic resistance in hospitals is at the formulary level. Formularies that restrict the use of antibiotics with resistance potential have been the only effective, widely applied control measure. At the formulary level, practitioners should also selectively prescribe antibiotics with minimal resistance potential to avoid neutralizing the effect of control measures. On a national level, antibiotics should be eliminated from animal feeds and animal products, which can find their way into human populations when people consume meat and poultry.

**TERMINOLOGY**

**Natural Resistance**

Natural resistance refers to the spectrum of an antimicrobial beyond its usual spectrum of activity. All antibiotics are effective against some organisms and are ineffective against others. The organisms against which a given antibiotic has no activity is naturally resistant. Therefore, natural resistance occurs with all antibiotics.

Twenty-five percent of pneumococci are naturally resistant to macrolides. This chromosomal resistance represents natural resistance and is not related to antibiotic use (see later). For example, gentamicin (Garamycin®, Schering) has no intrinsic activity against anaerobic organisms; thus, anaerobes are considered to be naturally resistant to gentamicin. Similarly, chloramphenicol has intrinsic activity against most bacterial microorganisms but no activity against Pseudomonas aeruginosa. Thus, Pseudomonas is said to be naturally resistant to the action of chloramphenicol. However, it is not natural resistance (which is outside the usual spectrum of activity of an antibiotic) that is usually meant when the topic is discussed.

**Acquired Resistance**

The topic of resistance generally refers to the acquired form, or the loss of an antimicrobial agent’s activity against an organism over time. An organism that was formerly sensitive to an antibiotic has become resistant, and the resistance is thus acquired. Examples include ampicillin-resistant *Escherichia coli*, ampicillin-resistant *Haemophilus influenzae*, penicillin-resistant *Moraxella catarrhalis*, macrolide, and trimethoprim–sulfamethoxazole (TMP-SMX [Bactrim®, Roche; Septra®, Monarch]–resistant *Streptococcus pneumoniae*).

Macrolide resistance to *S. pneumoniae* is interesting because it may be natural or acquired. Macrolides are potent inducers of acquired resistance to *S. pneumoniae*. This is in addition to the 20% to 25% of strains that are naturally resistant without exposure to macrolide antibiotics.

Acquired resistance may be further categorized as (1) absolute (high grade) or (2) relative (low grade).

**Absolute Resistance**

Absolute resistance is acquired, but the minimal inhibitory concentration (MIC) or minimal bacterial concentration
Antibiotic Resistance

(MBC) of the resistant strain is far beyond achievable body fluid concentrations when the drug is administered in the usual or even in high doses. An example is gentamicin-resistant *P. aeruginosa*. The usual MIC for gentamicin to susceptible strains of *P. aeruginosa* is 2 to 4 mcg/ml.

With strains of *P. aeruginosa* that have become highly resistant, the MIC may be 200 mcg/ml. Regardless of the dose of gentamicin administered, these concentrations cannot be achieved without toxic consequences. For this reason, high-grade, or absolute, resistance is the proper term for this variety of acquired antimicrobial resistance.

Relative Resistance

With penicillin, the MIC against certain strains of *S. pneumoniae* may increase somewhat. An increase in MIC is not synonymous with resistance. Strains with an increased MIC that are within the achievable therapeutic concentrations of the antibiotic being used should be considered as having diminished susceptibility, or *relative* resistance. An example is penicillin’s susceptibility to *S. pneumoniae*. Most organisms have breakpoints that measure pre-agreed-upon ranges of susceptibility and resistance. For most organisms, therefore, susceptibilities are reported as sensitive or resistant. Pneumococci, however, like some other organisms, have three zones of susceptibility:

- susceptible (less than 1 mcg/ml)
- intermediate (1–2 mcg/ml)
- resistant (2 mcg/ml or greater)

The dilemma becomes how to classify the intermediate strains. Are they relatively sensitive or relatively resistant? Are they intermediate in their sensitivity or resistance to the antibiotic in question?

The answer lies in the achievable serum and tissue concentrations generated by the antibiotic at the usual doses and dosing intervals. If the intermediate strain’s MIC (1–2 mcg/ml) is easily achieved with an antibiotic (e.g., ceftriaxone’s peak serum concentrations after a 1-g intramuscular dose are less than 200 mcg/ml), this would be far in excess of the range needed to eradicate these intermediate strains of pneumococci. Therefore, if the antibiotic can eradicate the intermediate strain at achievable serum concentrations, these intermediate strains should be grouped with the susceptible ones.

In contrast, resistant strains, depending on the level of resistance, may not be eliminated by the usual doses of an antibiotic. In such an instance, they should be termed *truly resistant*.

In the literature, pneumococcal resistance is often exaggerated in studies that combine the intermediate strains with the resistant strains. This occurs because most “penicillin-resistant” strains of *S. pneumoniae* are, in fact, isolates with an intermediate MIC range. If these isolates are grouped with susceptible strains—which is where they belong (because most beta-lactams can achieve concentrations far in excess of that needed to eradicate these intermediate strains)—they should be considered *susceptible*.

Cross-Resistance

Cross-resistance, which is usually plasma-mediated, refers to the resistance of antimicrobials of different classes by a single species of bacteria (e.g., resistant tuberculosis) and to the resistance of a species to a class of antimicrobials (e.g., fluoroquinolone-resistant *Salmonella typhi*) that would be resistant to the entire class of fluoroquinolones.4–8

FACTORS ASSOCIATED WITH RESISTANCE

Antibiotic resistance is not an inevitable result of the volume of antibiotic use. Many antibiotics have been used for decades without appreciable resistance problems, whereas others, even with minimal use, seem to induce resistance among one or two species.

It is difficult for most clinicians to understand that resistance can occur with tetracycline but does not occur with other members of the same class, such as doxycycline (e.g., Vibramycin®, Pfizer) or minocycline (Minocin®, Wyeth-Ayerst). Although tetracyclines as a group have the same mechanism of action and inactivation, this does not explain why tetracycline is likely to induce the genetic changes required to make an organism resistant to tetracycline (i.e., usually *Staphylococcus aureus* or *S. pneumoniae*). In contrast, doxycycline is still valuable after 40 years of worldwide use and has not been associated with resistance problems. It works reasonably well against *S. aureus*, excluding methicillin-resistant *S. aureus* (MRSA) strains, and works very well against all but highly resistant strains of *S. pneumoniae*. Minocycline has good activity against *S. pneumoniae* but excellent activity against *S. aureus* (including MRSA strains).

RESISTANCE BY ANTIBiotic CLASS

Among the second-generation cephalosporins, cefamandole nafate (Mandol®, Eli Lilly) is the only one associated with acquired resistance. Cefamandole resistance is limited to *H. influenzae* and *Enterobacter* species, although the drug retains its activity against other organisms in its usual spectrum of activity. Despite the third-generation cephalosporins, which have been used extensively for decades, only ceftazidime (Cep-taz® or Fortaz®, GlaxoSmithKline) has been associated with widespread resistance problems. Unrestricted use of cefotaxime (Claforan®, Aventis), ceftizoxime (Cefizox®, Fujisawa), cefoperazone (Cefobid®, Pfizer), and ceftriaxone (Rocephin®, Roche) has not resulted in pervasive resistance.

Some reports mention resistant isolates to each of these third-generation cephalosporins, excluding ceftazidime. In some cases, clonal spread of these resistant strains has occurred in limited geographical areas, but there has been no widespread resistance related to the use of these agents except for ceftazidime.

From a resistance standpoint, ceftazidime has had three effects. *P. aeruginosa* is one of the species associated with resistance to this drug. More recently, it has been appreciated that ceftazidime use has been associated with extended-spectrum beta-lactamases among a variety of microorganisms, particularly in strains of *Klebsiella*, *Serratia*, and *Enterobacter*. For reasons that are not clear, ceftazidime usage also increases
the prevalence of MRSA in settings when it is given in high volume. Ceftazidime does not induce methicillin resistance among strains of S. aureus but in some way permits the increase in the prevalence of MRSA strains.4,9

DOISING

In a general sense, underdosing of antibiotics that are given in sublethal concentrations sometimes predisposes them to the emergence of resistant strains. This is particularly true of antibiotics with a high resistance potential, but it is not true of antibiotics with a low resistance potential. Underdosing of tetracycline sometimes results in resistance, but underdosing of doxycycline does not.

The presence of high concentrations of bacteria being exposed to low concentrations of an antibiotic can also result in resistance, as occurs most often with abscesses. Most antibiotics do not penetrate abscesses efficiently, and, by definition, abscesses contain high numbers of microorganisms.

Given all the factors that may predispose antibiotics to resistance, the single most important factor is the antimicrobial agent itself. P&T committees and clinicians should view antibiotics as having a potential for resistance or as having little or no potential for resistance. When antibiotics are considered in this way, clinicians can selectively choose between two drugs, even in the same class, and can opt for the one with the lowest possible resistance potential. With all other factors being equal, amikacin (Amikin®, Geneva/Novartis) is preferable to gentamicin or tobramycin (e.g., TOBI®, Chiron; Nebcin®, Eli Lilly) from a resistance perspective alone. Meropenem (Merrem®, AstraZeneca) would be preferable to imipenem, all other things being equal, when a carbapenem is being used.4,6

STRATEGIES TO CONTROL RESISTANCE

Effective Strategies

The most fundamental way to minimize antibiotic resistance in the U.S. is to eliminate antibiotic supplementation—mainly tetracycline and quinolone derivatives—from animal feeds. These antibiotics are the least expensive, and they have the highest potential for resistance. These resistant strains make their way into human populations when people consume animal and poultry products.

An important means of minimizing the spread of resistant strains is an effective infection-control program. Much of the world’s problems of resistance are caused by the clonal spread of a single strain across countries or continents. Effective measures can limit the spread of these resistant organisms to the location of origin. The most highly resistant organisms do not pose a threat to the public health if their spread is contained.

Ineffective Strategies

Many strategies for decreasing resistance have been proposed, such as decreasing unnecessary antibiotic use. This makes good general medical sense but does not necessarily reduce resistance unless the antibiotics being curtailed carry a potential for resistance.

It is commonly thought that rotating formularies, either in intensive-care units (ICUs) or in hospitals, might temporarily ameliorate the problem or might worsen it. Rotating formularies indicate that the proponents of these plans do not understand the importance of resistance potential, which is, in large part, agent-specific. If antibiotics that are introduced into the rotation scheme have a high resistance potential, the problem of resistance might worsen or a switch might be made to a more virulent, highly resistant organism.

The other problem with ICU-restricted formularies is the notion that any resistance problems would be restricted to the ICU; this is not the case. The hospital should be viewed as a single entity or biome. Patients from the ICU are transferred to other floors and take their resistant organisms with them. Patients from the general hospital wards also are returned to the community, taking the organisms outside the hospital.

The reverse is true as well. It is amazing to see resistant organisms arriving from the community, with no one able to explain how these organisms find their way into patients who have not been recently hospitalized. Actually, these patients have been in contact with others who have been hospitalized; the resistant organisms are completing their cycle and are being reintroduced into hospitals from the community, albeit in an indirect fashion.9–11

FORMULARY RESTRICTION

More permanent, less dangerous, and better than formulary rotation is formulary restriction. The restricted formulary is the only method that has been shown to decrease resistance. The cornerstone of this concept is based on the notion that resistance is agent-specific and is not related to volume, duration of use, or antibiotic class per se.

Antibiotics that have resistance potential should not be on formularies, or they should be highly restricted to minimize their effect on the hospital flora. Other agents should be used in their place and should constitute the unrestricted antibiotics in the hospital’s formulary. It makes little sense to restrict third-generation cephalosporins if the problem is P. aeruginosa and if the problem is related to ceftazidime. Ceftazidime should be restricted, and the other third-generation cephalosporins should remain unrestricted. Other effective antipseudomonal agents should replace ceftazidime as the hospital’s anti-pseudomonal cephalosporin or beta-lactam.

If gentamicin-resistant P. aeruginosa is present in a hospital, simply substituting amikacin for gentamicin might lessen the problem but might not eliminate it. If the resistance is not decreased by a single-drug substitution at the formulary level, then the P&T committee, after communication with the infectious diseases department, should review other antipseudomonal drugs on the formulary to determine whether other drugs that affect the same organism are being used in high volume. For example, if ceftazidime or imipenem (Primaxin®, Merck) is being used in high volume, the situation cannot be corrected.

After a formulary change, it can take six, nine, or 12 months for the hospital microbial flora to readjust to the usage patterns of antibiotics, which will be reflected in improved susceptibility patterns over time with respect to the resistant organism.4,6,12
**SUMMARY**

Single-agent substitution may be helpful for specific situations involving resistance. If this approach is unsuccessful, all drugs with a primary spectrum of activity against a resistant organism and that are being used in high volume in the hospital should be reviewed. After the review, the P&T committee should make formulary changes by substituting low-resistance-potential antibiotics, class by class, for each of the agents involved. In this way, resistance problems should be minimized for long periods of time.

Regardless of the antibiotic used, there will always be episodic outbreaks of resistant organisms. The infection-control section should make every attempt to minimize the clonal spread of these organisms within the institution. Given our current state of understanding, hospitals can be made as resistance-free as possible when infection-control sections work hand in hand with infectious disease departments and P&T committees.

**REFERENCES**