Principles of Antibiotic Formulary Selection for P&T Committees
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Part I: Antimicrobial Activity

Antimicrobial agents that are being considered for inclusion on a formulary should have a high degree of activity against the pathogens they are intended to treat. If an antimicrobial is going to be used primarily for urinary tract infections (UTIs) or urosepsis, its spectrum of activity should be greatest against aerobic gram-negative bacilli and enterococci because these two pathogen groups are the primary causes of UTIs in hospitalized patients. Antibiotics that are used to treat UTIs do not require activity against respiratory pathogens (e.g., pneumococci) or against organisms that affect the skin (e.g., Staphylococcus aureus). Furthermore, because anaerobes are not uropathogens, anti-anaerobic activity is not needed in drugs whose intended primary use is for UTIs or urosepsis.

Frequently, pharmaceutical companies present data to P&T committees showing a wide range of activity, often against organisms that are either clinically irrelevant or so rare as to be clinically unimportant. These data are often displayed against organisms that are almost always colonizers and that do not cause infection and, therefore, do not warrant treatment.

Ordinarily, organisms that colonize respiratory secretions, wounds, urine, feces, or skin are not treated. Therefore, antibiotics that have a high degree of activity against these organisms might be suitable for treating infection but are inappropriate and not cost-effective for use against colonizing organisms. Most organisms that have been recovered from the sites mentioned are indeed colonizers and cause infection only infrequently (e.g., Citrobacter freundii, Enterobacter agglomerans, Stenotrophomonas maltophilia, Burkholderia cepacia, and so on). Other organisms, such as methicillin-resistant S. aureus (MRSA) or vancomycin-resistant enterococci (VRE), do cause infection, but more than 90% of the time they colonize the skin, respiratory secretions, urine, or feces.

MINIMAL INHIBITORY CONCENTRATION

A company’s pharmaceutical literature might also emphasize differences in the minimal inhibitory concentration (MIC) of its products compared with that of the competitor. Remember, the MIC is an in vitro determination and is an important—but not the only—measure of an antibiotic’s activity. The MIC is isolated and meaningless if it is taken out of the clinical context.

It is a popular misconception that drugs with a lower MIC are more effective, or that they kill more efficiently or quickly, than drugs with a higher MIC if an organism is sensitive to both types of antibiotics. If an organism is sensitive, all antibiotics with an MIC of 2, 0.2, or 0.02 mcg/ml kill at precisely the same rate with the same efficacy and effectiveness. There is no advantage to paying a premium for drugs with the lowest MIC.

Occasionally, a pharmaceutical firm’s promotional literature might present differences in MICs as if they were important when, in fact, the differences are so small as to be unimportant. If an antibiotic has an MIC of 0.3 mcg/ml, it should not be assumed to be inferior to an agent with an MIC of 0.03 mcg/ml; these concentrations are very low and should be easily achievable in most body tissues in comparisons of sensitive antibiotics.1

The MIC should also be considered in relation to achievable blood levels. The ratio of peak serum concentration to MIC is a popular misconception that drugs with a lower MIC are more effective, or that they kill more efficiently or quickly, than drugs with a higher MIC if an organism is sensitive to both types of antibiotics. If an organism is sensitive, all antibiotics with an MIC of 2, 0.2, or 0.02 mcg/ml kill at precisely the same rate with the same efficacy and effectiveness. There is no advantage to paying a premium for drugs with the lowest MIC.

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Antibiotic Formulary Selection

Table 1  Antibiotic Organism Combinations for Which in Vitro Susceptibility¹ Testing Is Unreliable

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>“Sensitive” Organism</th>
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<tbody>
<tr>
<td>Penicillin</td>
<td><em>Haemophilus influenzae</em>, <em>Yersinia pestis</em></td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole (TMP–SMX) (Bactrim®, Roche; Septra®, Monarch)</td>
<td><em>Klebsiella</em>, <em>enterococci</em>, <em>Bartonella</em></td>
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<tr>
<td>Polymyxin B</td>
<td><em>Proteus</em>, <em>Salmonella</em></td>
</tr>
<tr>
<td>Imipenem (Primaxin®, Merck)</td>
<td><em>Stenotrophomonas maltophilia</em>²</td>
</tr>
<tr>
<td>Gentamicin (Garamycin®, Schering)</td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Vancomycin (Vancocin®, Eli Lilly)</td>
<td><em>Erysipelothrix rhusiopathiae</em></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td><em>Streptococci</em>, <em>Salmonella</em>, <em>Shigella</em></td>
</tr>
<tr>
<td>Clindamycin (Cleocin®, (Pharmacia &amp; Upjohn)</td>
<td><em>Fusobacteria</em>, <em>Clostridia</em>, <em>enterococci</em>, <em>Listeria</em></td>
</tr>
<tr>
<td>Macrolides</td>
<td><em>Pasteurella multocida</em></td>
</tr>
<tr>
<td>First-generation and second-generation cephalosporins³</td>
<td><em>Salmonella</em>, <em>Shigella</em>, <em>Bartonella</em></td>
</tr>
<tr>
<td>All antibiotics except vancomycin</td>
<td><em>MRSA</em>⁴</td>
</tr>
<tr>
<td>Minocycline (Minocin®, Wyeth-Ayerst), quinupristin/dalfopristin (Synercid®, Rhone-Poulenc Rorer/Avensit), and linezolid (ZyvoxTM, Pharmacia)</td>
<td></td>
</tr>
</tbody>
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MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

¹ In vitro susceptibility does not predict in vivo activity, and susceptibility data cannot be relied on to guide therapy.

² Formerly called *Pseudomonas* and *Xanthomonas*.

³ Cefoperazone is the only cephalosporin with clinically useful anti-enterococcal activity (*Enterococcus faecalis*, not *Enterococcus faecium* [VRE]).

⁴ Despite apparent in vitro susceptibility of many antibiotics against MRSA, only vancomycin, quinupristin/dalfopristin, linezolid, and minocycline are effective in vivo.


appear to be sensitive *in vitro* but are ineffective *in vivo* for the treatment of *Bartonella* infections. Similarly, TMP–SMX appears to be sensitive *in vitro* but is relatively ineffective *in vivo*. Penicillin is commonly reported as being effective against *Haemophilus influenzae* but is ineffective *in vivo*. Streptococci are usually reported as being sensitive to aminoglycosides but, in fact, have no anti-streptococcal activity unless they are combined with another agent. For this reason, penicillin plus gentamicin is effective in treating streptococcal endocarditis. Gentamicin (e.g., Garamycin®, Schering) alone, although sensitive by *in vitro* testing, is ineffective clinically and works only in combination because of the synergy between penicillin and gentamicin (Table 1).⁵–¹⁰

**BACTERIOSTATIC AND BACTERICIDAL ANTIBIOTICS**

Pharmaceutical companies sometimes underscore the purported advantages of *bactericidal* antibiotics (destructive to organisms) over *bacteriostatic* antibiotics (inhibitory to the growth of organisms); “bactericidal” and “bacteriostatic,” however, are *in vitro* determinations. Both categories of drugs kill with equal speed and equal efficacy if the organism is sensitive to both types.

Bactericidal drugs have no advantage over bacteriostatic antibiotics except in three situations: febrile neutropenia, meningitis, and endocarditis. Even in these areas, there are important exceptions. For example, chloramphenicol (e.g., Chloromycetin®, Parke-Davis/Pfizer) has been successfully used for decades in the treatment of meningitis, even though it is a bacteriostatic antibiotic by *in vitro* determinations. As stated earlier, susceptibility is concentration-dependent. According this perspective, then, it can be shown that penicillin—in a low concentration—acts as a bacteriostatic agent and that chloramphenicol—in a high concentration—acts as a bactericidal agent, further blurring the artificial distinction between “cidal” and “static” antimicrobials. For patients with endocarditis, in whom bacteriostatic drugs are preferred, they are by no means the only way to effectively treat endocarditis. For example, Q fever and *Legionella* endocarditis have been treated successfully with static agents.

Some antibiotics work well both bacteriostatically and bactericidally, depending on the *in vitro* methodology used in testing. Linezolid (ZyvoxTM, Pharmacia), for instance, has bactericidal as well as bacteriostatic activity. Because it doesn’t matter whether an antibiotic is bactericidal or bacteriostatic, this is a...
moot point. Linezolid has been used to treat MRSA endocarditis with good results. The clinical outcome is the most important determination; it is immaterial whether endocarditis is cured bacteriostatically or bactericidally.

Because microbiological aspects of susceptibility testing are complex with many clinical nuances, P&T committees should rely on input from infectious disease experts by including an infectious disease clinician in the decision-making process; it is imperative that the clinician be a specialist in antimicrobial therapy. If possible, such individuals should participate as P&T committee members or should be available as consultants. However, clinicians from various disciplines, including infectious disease, who have been involved in antimicrobial drug trials should not automatically be viewed as “experts.” An authority in antibiotics will have undertaken specific training in microbiology and infectious disease and will have demonstrated expertise in the field of antimicrobial therapy; he or she will not have experience only in the treatment of infectious disease.2,3,7

REFERENCES
2. Johnson CC. In vitro testing: Correlations of bacterial susceptibility, body fluid levels, and effectiveness of antibacterial therapy.