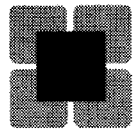

Newer antibiotics and resistant bacteria

IN THE 50 years that antibiotics have been available for clinical use, gram-negative bacteria have become important causes of hospital-acquired infection.[1] *Pseudomonas aeruginosa* is now the leading cause of nosocomial lower respiratory infections, followed by *Klebsiella* sp, *Staphylococcus aureus*, and *Enterobacter* sp.[2] Although coagulase-negative staphylococci and *Staphylococcus aureus* account for about 27% of surgical wound isolates, and enterococci for another 11%, about 40% of the wound pathogens are aerobic gram-negative bacilli. A third to half of nosocomial bacteremias are due to gram-negative bacilli.[3] They are also important pathogens in neonatal and postoperative meningitis, fulminant pyelonephritis, burn-wound infections, and infections in neutropenic patients.

■ *See Knapp and Washington (pp 161–166)*

Because of the profound influence of infections due to gram-negative bacilli on hospital practice, major efforts have been made to find new drugs effective against them. Aminoglycoside antibiotics are active against most gram-negative bacilli, but nephrotoxicity and ototoxicity limit their use. The cephalosporins that were available in the '60s and early '70s are not active against many nosocomial gram-negative pathogens. Thus, antibiotic research and development have focused on identification of safe, expanded-spectrum β-lactam agents like third-generation cephalosporins (cefotaxime, cefoperazone, ceftizoxime, ceftriaxone), extended-spectrum penicillins (piperacillin, mezlocillin, azlocillin, timentin/clavulanic acid), monobactams (aztreonam), and carbapenems (imipenem/cilistatin).

ENHANCED ACTIVITY OF NEWER ANTIBIOTICS

The newer cephalosporins represent a significant breakthrough because they are active against many gram-negative bacteria (such as *Serratia*, *Citrobacter*, and *Enterobacter* sp), which are inherently resistant to the other penicillin and cephalosporin antibiotics but are much safer to use than aminoglycosides. Their cerebrospinal fluid penetration far exceeds that of aminoglycosides and older β-lactam drugs, making them extremely important tools for the treatment of gram-negative meningitis.[4]

The ureidopenicillins have enhanced activity against *Pseudomonas* and *Klebsiella* sp.[5,6] Although aztreonam is not as active as some of the third-generation cephalosporins against *Pseudomonas* and *Enterobacter* sp, it can be used in the treatment of infections due to other gram-negative bacteria. Aztreonam is potentially of value for the treatment of gram-negative infection in the penicillin-allergic patient.[7] Imipenem is an important alternative to combination antibiotic therapy for infections due to mixed microbial flora[8] and for those due to gram-negative bacilli resistant to other antibiotics.

A major reason for the enhanced gram-negative spectrum of the newer β-lactam antibiotics is their stability against the activity of drug-inactivating enzymes (β-lactamases) produced by bacteria. Unfortunately, this feature may ultimately allow the emergence of resistant organisms,[9] as use of these agents may result in hyperproduction of chromosomally determined β-lactamase, or less frequently, spread of plasmid-determined β-lactamases with altered kinetic properties.[10]

In this issue of the *Cleveland Clinic Journal of Medicine*, Knapp and Washington document the presence of significant numbers of *Citrobacter freundii*, *Enterobacter aerogenes*, and *Enterobacter cloacae* isolates resistant to broad-spectrum penicillins, cephalosporins, and aztreonam. This is an important and striking finding since earlier studies indicate excellent in vitro activity of these drugs against most gram-negative species. Although some of the differences in susceptibility may be due to methodology, it is likely that increasing use of these agents, all of which select for resistant bacteria

after inhibiting growth of susceptible strains, has allowed this trend to emerge. Serial testing of strains isolated from patients undergoing antibiotic therapy and detailed studies of hospital antibiotic use would be necessary to confirm this hypothesis.

CLINICAL IMPLICATIONS

These results nonetheless have important implications for the practicing physician. Recently advocated as drugs of choice for monotherapy of serious infections, expanded spectrum penicillins, third-generation cephalosporins, and aztreonam can no longer be used with confidence when *Enterobacter* and *Citrobacter* sp are likely to be the cause of a life-threatening infection.

Major questions remain in the treatment of serious infections due to gram-negative bacilli. The site of infection and adequacy of adjunctive treatments, such as surgical debridement, influence the observed efficacy of any therapy. If therapeutic concentrations cannot reach the site of infection, a longer course of antibiotics is required and there may be further opportunities for the development of resistance. Likewise, altered host defenses will undoubtedly influence individual responses to antibiotic therapy. As Knapp and Washington point out, the utility of combination therapy (usually a β-lactam with an aminoglycoside antibiotic) in improving clinical response and inhibiting the emergence of resistant organisms is not clear. Most of the information supporting combination therapy of gram-negative bacterial infections was generated during trials of empiric antibiotic use in febrile neutropenic patients. Studies attempting to correlate in vitro antibiotic synergy with improved clinical response have been performed in animal models of *Pseudomonas aeruginosa* pneumonia, but the findings have been difficult to duplicate in humans.[11]

There is a great deal of interest in the possibility that new oral fluoroquinolone agents such as ciprofloxacin may replace intravenous therapy for a variety of conditions. There is no question that they are extremely useful in the treatment of some infections due to organisms that otherwise would require therapy with a parenteral antibiotic. Caution should be exercised here, however, as the serum concentrations of most oral quinolones is quite low.[12] Subtherapeutic tissue levels at the site of infection might lead to failure of therapy, particularly in areas of poor perfusion or when large numbers of bacteria are present.

Although fluoroquinolones are effective in the therapy of uncomplicated urinary tract infections, skin and soft tissue infections, and respiratory tract infections due to susceptible organisms, an antibiotic with a narrower spectrum of action may be capable of the same degree of clinical success. The issues remaining in the oral treatment of deep-seated infections will not be easily resolved because of inherent difficulties in determining the in vivo "inoculum," the adequacy of antibiotic penetration, and the effectiveness of host defenses at these sites.

Both the carbapenem and the quinolone groups of antibiotics have the potential to retain their utility in single-agent treatment of infections because of their unique sites and mechanisms of action. However, patients treated with imipenem or ciprofloxacin are not protected from the emergence of resistant organisms or from the development of suprainfection. At least 15% of *Pseudomonas aeruginosa* isolates become resistant to imipenem during therapy,[13] and colonization and suprainfection with *Pseudomonas maltophilia* may be problematic. Resistance to imipenem-cilistatin may be mediated through alterations in porins, which allow transport of the antibiotic molecule across the cell membrane.[14] Resistant strains of *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Staphylococcus aureus* have caused relapse of osteomyelitis, pneumonia, and urinary tract infections in some patients treated with oral fluoroquinolones for long periods.[15]

We are fortunate that a large number of safe and effective antibiotics are available for clinical use. Bacterial resistance, however, has not been eliminated by these drugs, and control of the resistance problem will not occur through development of new agents—there are no "magic bullets." Instead, efforts to limit the spectrum and duration of antibiotic therapy, to preserve the normal microbial flora, and to augment host defense mechanisms should be encouraged. Further developments in the correlations between in vitro testing and the outcome of clinical therapy of infections would be useful. In the meantime, judicious use of these powerful new antibiotics should improve the outcome in individual patients without excessive contribution to the prevalence of resistant organisms.

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