ic
INFECTION CONTROL

EDITORIAL

Dilemmas of the Beta-Lactam Explosion

The development of new and more potent antimicrobics over the past few years has been profligate, and has surpassed the absorption threshold of the average clinician. This proliferation has not been limited to the new drugs with their empirically-determined advantages and shortcomings. Our understanding of principles and mechanisms of antimicrobial action, mechanisms of microbial resistance, means of overcoming microbial resistance, and related concepts has expanded at an equally rapid rate. This "explosion" of new antimicrobics and information not only poses dilemmas for clinicians; the laboratorian and infection control practitioner are also faced with new problems.

The beta-lactam antibiotics, because of their clinical safety, have led the development parade and serve as excellent examples of the dilemmas we face. The recently released "third generation" cephalosporins (cefoperazone, cefotaxime, and moxalactam) are markedly more active against most microbes than earlier members of this family. Although most third generation compounds are similar in many respects, there are some significant differences among them. In the antimicrobial spectrum, for example, moxalactam exhibits the best *in vitro* activity against *Bacteroides fragilis;* cefoperazone has the highest activity against *Pseudomonas aeruginosa;* and cefotaxime is superior against non-enterococcal streptococci, *Haemophilus influenzae*, and gonococci—including beta-lactamase-producing strains. Although cefatoxime has greater activity against staphylococci than the other two drugs, this activity is still less than that of cephalothin. Like cefoxitin, cefotaxime and moxalactam exhibit remarkable stability to most bacterial beta-lactamases. Cefoperazone is less stable, but still superior to the second generation cephalosporin, cefamandole.

The pharmacokinetics of the three drugs also differ. There is some evidence to indicate that cefotaxime and moxalactam may enter the cerebrospinal fluid in effective concentrations (10-30% of peak serum concentrations)—a characteristic not present in earlier cephalosporins. These new beta-lactam antibiotics significantly increase the clinician's potential to treat a greater number of serious infections with a single safe drug. But, at the same time, the parameters that must be considered for rational drug selection and use have become more numerous and complex. One cannot assume that all "third generation" cephalosporins are alike and can be used interchangeably —a principle that will be more striking as other newer cephalosporins become available. Nor can one assume that the latest cephalosporins are superior—or even comparable—to the older drugs in all situations, e.g. staphylococcal infections, for which the "first generation" cephalosporins remain the drugs of choice. Cost is another important consideration in selection of drugs, and many infections will respond equally well to the less expensive, older cephalosporins.

There is a tendency among many infectious disease specialists to restrict the usage of the new potent antimicrobics, thereby reserving them for very select situations. One of the arguments used to support this practice is: Widespread use of these drugs will lead to development of resistance, and thus render these antimicrobics useless for serious infections. An example of this was the widespread restriction of amikacin. Such phenomena were well documented more than a decade ago, but in recent years development of resistance to the newer antimicrobics has been spotty, not widespread, and essentially unrelated to the extent of use of a drug. This does not imply that indiscriminate use of these drugs should be condoned. On the other hand, the use of these very active, but relatively safe, drugs probably should not be restricted when careful consideration of all parameters indicates one of them to be appropriate.

The clinical microbiologist faces a dilemma from the standpoint of antimicrobic susceptibility testing. The old "class" representative concept of susceptibility testing

(testing a single member of a class of antimicrobics is representative for all members of the class), is rapidly falling by the wayside. This concept worked well with the "first generation" cephalosporins, for which cephalothin was the class representative. With the "second generation" cephalosporins, the spectra of cefamandole and cefoxitin (a cephamycin) were too different to be treated alike. The currently available "third generation" cephalosporins require at least two separate tests: cefoperazone, and either cefotaxime or moxalactam—cefotaxime is preferred for technical reasons in disk diffusion testing, but both cefotaxime and moxalactam show sufficiently similar spectra against facultative gram-negative bacteria that either may be used. (As the newer drugs in this class become available, however, more drugs may need to be individually tested because of their unique activities.) Therefore, to test the currently available cephalosporins, at least five drugs would be appropriate. This is quite impractical and expensive, yet no obvious solution to this dilemma is at hand. As the newer cephalosporins reach the market, as well as the other beta-lactams of the penicillin family, e.g. azlocillin, mezlocillin and piperacillin, this problem will be compounded.

Which drugs should a laboratory test routinely? At this time a compromise appears to be the most practical solution. Since the usage of different antimicrobics frequently varies from locale to locale (and even among institutions in the same locale), it would be prudent for each laboratory to determine the usage patterns of the physicians it serves, and after consultation with the pharmacy and clinical staff, select two or three cephalosporins for routine testing that best represent the current local pattern of clinical usage.

Finally, these new and potent antimicrobics will also affect the activities of the hospital epidemiologist. Antimicrobics may play a dual role in predisposing patients to nosocomial infections: 1) They reduce the susceptible normal microbial flora of the host, thus allowing less hospitable organisms to fill the void; and 2) They tend to select resistant microbes to colonize and infect the host. For example, in a study of colon resections in our hospital from 1972-1974, the post-operative wound infection rate was 19.4% in 103 patients receiving no prophylactic antibiotics, and was 19.1% in 94 patients receiving cephalothin only as prophylaxis. The striking difference was in the organisms isolated from these infections. Microbes resistant to cephalothin were isolated from 25% of infections in the no-antibiotic group, but from 83% of the cephalothin group. Furthermore, the mean post-operative hospital stay was 11.0 days in the former group, compared to 14.8 days for the latter—a significant difference. Thus, in this patient population, the use of cephalothin prophylaxis had no effect on the incidence of wound infections, but the selection of resistant organisms by the cephalothin was very apparent.

Infection control practitioners must be alert to the influences that antimicrobics exert on nosocomial infections in their institutions. This becomes increasingly important with the newer antimicrobics because of their broader spectrum and greater potency. Since many of these agents are refractory to bacterial beta-lactamases, the epidemiology staff should be alert to the possible emergence of new patterns of resistance similar to those encountered after the introduction of the broad-spectrum aminoglycosides.

Peter C. Fuchs, Ph.D., M.D.
St. Vincent Hospital and Medical Center
9205 S.W. Barnes Road
Portland, Oregon 97225

Ronald N. Jones, M.D.
Kaiser Permanente Hospital
10200 S.E. Sunnyside Road
Clackamas, Oregon 97015

(Address reprint requests to Dr. Fuchs.)