This issue is the millennium issue of the Medical Clinics of North America and is dedicated to the topic antibiotic therapy. Antibiotic therapy has evolved during the past several decades and much has been learned about the optimal application of antimicrobial therapy in infectious diseases. Our understanding and experience has taken us from the over-simplified notion of drug of choice, i.e., “what drug for what bug,” to an appreciation of other factors critical in the selection of an antimicrobial agent. Because this is a millennium issue, I have tried to achieve a global perspective on antimicrobial therapy. Accordingly, the contributors are recognized world authorities and opinion leaders in antimicrobial therapy from several countries.

Currently, we appreciate that the selection of an antibiotic rests not only upon its antimicrobial spectrum, but also upon its pharmacokinetic and pharmacodynamic attributes, resistance potential, safety profile, and cost. Antimicrobial therapeutics have progressed from the era of “the minimal inhibitory concentration (MIC) wars,” where drug superiority was thought to be related to the antimicrobial with the lowest MIC, to the present time. Now we know that an interplay of host and drug factors determines clinical outcome, which is a better yardstick than in vitro comparisons. Pharmacodynamic considerations have helped to optimize dosing regimens, based on an understanding of antibiotic concentration/time-dependent killing kinetics. Pharmacodynamics also takes into account postantibiotic inhibition of bacteria when the antibiotic is no longer present. The postantibiotic effect (PAE) helps to explain why some antibiotics are effective even if antibiotic concentrations drop below the MIC of the pathogen near the end of the dosing interval.

Pharmacodynamic principles have sometimes been misapplied to antibiotic therapy for promotional purposes. Clinicians should be reminded that pharmacodynamic parameters are in vitro calculations that may or may not relate to an antibiotic’s clinical efficacy in vivo. Pharmacodynamics have also been misapplied to predicting resistance potential, which has caused some to confuse regrowth with resistance. The most important contribution of pharmacodynamic concepts to antimicrobial therapy has been in characterizing antibiotic action as
dose- or time-dependent, which has had an important impact on optimizing antibiotic dosing regimens.

Antibiotic side effects are important from a patient, hospital, and legal standpoint. Drug safety profiles appropriately affect prescribing habits and are an important factor in antibiotic selection. Our knowledge and understanding of adverse side effects has increased in recent years through the introduction of several new antibiotic agents. Although some side effects are related to antibiotic class, most side effects are agent specific. The most common antibiotic class side effects are cross allergenicities within a class of antibiotics. However, agent specific side effects are the rule and are related to individual antimicrobial agents, e.g., photosensitivity reactions occur with tetracycline but rarely, if ever, with doxycycline or minocycline. Phototoxicity is associated with sparflaxacin, but is not a problem with other fluoroquinolones. Among the carbapenems, imipenem may cause seizures, but meropenem does not. These few examples illustrate the point that nonallergic side effects are, in the main, agent specific, and not class related.

Many new antibiotics have been introduced over the past several years, which is an additional justification for a millennium issue on antimicrobial therapy. Several antibiotics have been withdrawn or their use discouraged because of serious agent specific side effects. Among the β-lactams, moxalactam, but not other β-lactams, i.e., cefamandole, cefotetan, cefoperazone, has been associated with serious bleeding problems. Among the fluoroquinolones, serious side effects have resulted in the withdrawal from the market, or greatly curtailed use of temafloxacin, sparflaxacin, grepafloxacin, and trovafloxacin. The lesson learned from the trovafloxacin experience suggests that newly introduced antimicrobial agents, unless they have some unique attributes not possessed by currently available agents, should not be placed too quickly on hospital formularies. Before being added to hospital formularies for general use, a trial period of 2 years after a new antibiotic has been released for general use seems prudent. This period is sufficient to determine if serious side effects or resistance problems will occur. The old adage of “be not the first and be not the last” seems appropriate for newly introduced antibiotics being considered for hospital formulary inclusion. Experience has demonstrated that side effect and resistance problems, if they are going to occur, will be apparent within the first 2 years after their release for general use.

On the positive side, the modification of some drugs has decreased side effects and improved the tolerability of these agents. Newer formulations of amoxicillin/clavulanic acid with lower clavulate concentration, that permits once-daily dosing and once-daily extended action clarithromycin, are examples of antibiotic modifications that have reduced/eliminated the gastrointestinal side effects associated with the older formulations of these antibiotics.

Decades of experience preceding the millennium has also taught us much about antimicrobial resistance. The excessive, and in some cases, inappropriate use of some antibiotics has resulted in a growing concern about antimicrobial resistance. Antimicrobial resistance is a problem particularly with aerobic gram-positive cocci and some aerobic gram-negative bacilli. The past few years have witnessed an increase in the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). During this time, MRSA and VRE have become more prevalent but not more resistant. Vancomycin, for example has increased the prevalence of resistant enterococci, i.e., E. faecium (VRE) but E. faecalis resistance has not increased. Resistance among aerobic gram-negative bacilli is most common with Enterobacteriaceae, but is of particular concern with Enterobacter, Klebsiella, and Pseudomonas aeruginosa. Other organisms...
traditionally have been resistant to multiple antibiotics, including *Acinetobacter baumannii* and the nonaeruginosa pseudomonads, i.e., *Stenotrophomonas maltophilia,* and *Burkholderia cepacia.* During the past decade, *A. baumannii* has not become more resistant to antimicrobials but, rather, has become more prevalent. Extended spectrum β-lactamases (ESBLs) are becoming an increasing problem and occur with aerobic gram-negative bacillary infections treated with ceftazidime, or most recently, ciprofloxacin.

Penicillin resistance among *Streptococcus pneumoniae* has received much attention in recent years. Fortunately, resistance among pneumococcal strains is of the largely intermediate variety, i.e., “relative resistance,” which is still treatable using the usual doses of β-lactams in all but a few very circumstances. Fortunately, truly highly penicillin-resistant strains of *S. pneumoniae* remain rare, but overuse of some β-lactam antibiotics is probably responsible for initiating/perpetuating pneumococcal resistance that has occurred during the past few decades. Antibiotic resistance has caused much confusion among clinicians because “relatively resistant” *S. pneumoniae* strains are also “relatively sensitive.” Therefore, pneumococci may be considered either as relatively resistant or relatively sensitive pneumococci. If “intermediate strains” are grouped with the *resistant* pneumococci, i.e., MIC ≥2 μg/mL, then it appears that penicillin-resistant pneumococci are very common. Conversely, if the “intermediate strains” are grouped with *sensitive* strains, then the incidence of penicillin resistant pneumococci is not so common. The preferential use of anti-pneumococcal antibiotics that act intracellularly, e.g., doxycycline, respiratory quinolones, etc. may halt or reverse the trend of increasing pneumococcal penicillin resistance. At the millennium, clinicians have several antibiotics that are effective against penicillin resistant *S. pneumoniae,* e.g., doxycycline, clindamycin, levofloxacin, vancomycin, quinupristin/dalfopristin, or linezolid.

Fortunately, resistance among anaerobes, most importantly, *Bacteroides fragilis,* has not been a problem. Resistance is also not a problem with *Rickettsia, Chlamydia,* spirochetes, intracellular pathogens, or atypical respiratory pathogens, e.g., *Mycoplasma pneumoniae,* *Legionella,* and *C. pneumoniae.* Beyond the millennium, we must use antibiotics more carefully. Most importantly, clinicians should preferentially select antibiotics associated with little or no resistance potential.

Experience has also taught that antibiotic resistance is not related to volume or years of antibiotic use, nor is it related to antibiotic class. The historical review of antimicrobial resistance demonstrates antibiotic resistance is agent specific and is independent of the factors mentioned. Many antibiotics have been used extensively for decades without incurring widespread resistance argues against volume or years of usage as primary determinants of resistance; examples include nitrofurantoin, doxycycline, and all third-generation cephalosporins, except ceftazidime. In each antibiotic class, specific agents are associated with antibiotic resistance, but antibiotic resistance is not a class phenomenon. With tetracyclines, *S. aureus* and *S. pneumoniae* resistance has been a problem only with tetracycline, but not with doxycycline or minocycline. Among the aminoglycosides, gentamicin has been associated with *Pseudomonas aeruginosa* resistance, but not amikacin. Among the carbapenems, imipenem has been associated with *P. aeruginosa* resistance, but this has not been the case with meropenem. Among the second-generation cephalosporins, cefamandole has been associated with *Hemophilus influenzae* and *Enterobacter* resistance problems, but this has not been the case with all of the other second-generation cephalosporins, i.e., cefotixin, cefotetan, or cefuroxime.

Antibiotic resistance is often blamed on certain antibiotic classes, e.g., third-
generation cephalosporins and fluoroquinolones. Resistance among the third-generation cephalosporins has not been a problem with any third-generation cephalosporin, i.e., cefotaxime, ceftizoxime, cefoperazone, or ceftriaxone except ceftadizime. Virtually all third-generation cephalosporin resistance problems remain limited and related only to ceftazidime. Ceftazidime has been associated with *P. aeruginosa* resistance, and, more recently, with the induction of ESBLs among aerobic gram-negative bacilli, particularly *Klebsiella*. Excluding norfloxacin and nalidixic acid, fluoroquinolone resistance problems have been associated with ciprofloxacin use. Following the introduction of ciprofloxacin, there have been no important resistance problems with any other quinolones, e.g., tadalafiloxacin, ofloxacin, levofloxacin, sparfloxacin, grijofloxacin, trovafloxacin, gatifloxacin or gemifloxacin. The myth that fluoroquinolone use, per se, will result in widespread resistance is false. Even the limited use of ciprofloxacin may result in resistance problems, but the unrestricted use of any of the other quinolones, e.g., levofloxacin, does not. As should be readily apparent from a historical analysis, antibiotic resistance is agent specific and is not related to antibiotic volume, years of use, or class. Recently, pharmacodynamic calculations have been suggested as predictors of fluoroquinolone resistance. Pharmacodynamic parameters may predict regrowth, but regrowth is not synonymous or to be confused with resistance. Antibiotics associated with resistance problems develop resistance regardless of their PK/PD ratios, and antibiotics with little or no resistance potential, e.g., doxycycline, levofloxacin, have not been associated with resistance regardless of their PK/PD ratios. Antibiotics with so-called optimal pharmacodynamic ratios have not been shown to predict or prevent resistance.

Global control of antibiotic resistance is best approached by eliminating resistance-inducing antibiotics from animal feeds. Unfortunately, the two most common antibiotics added to animal feeds worldwide, i.e., ciprofloxacin and tetracycline, have a high-resistance potential. At the hospital level, the control of resistance is best attacked by antibiotic formulary restriction. Effective resistance control measures include limiting the hospital formulary to exclude/limit antibiotics known with a high-resistance potential, e.g., ciprofloxacin, imipenem, and ceftazidime. Other drugs may need to be restricted for other reasons, e.g., vancomycin, to prevent an increase in the prevalence of *E. faecium* (VRE). Established resistance problems may be limited by effective infection control measures and by the substitution of equivalent antibiotics with low resistance potential, so-called “vacuum cleaner” antibiotics, that will restore antibiotic susceptibilities in institutions after months of replacement usage. For example, if ciprofloxacin is determined to be the primary cause of resistance problems in an institution, then levofloxacin may be substituted in its place. Similarly, if ceftazidime is determined to be the primary cause of resistance in an institution, then the replacement of ceftazidime by cefepime as the “vacuum cleaner” replacement antibiotic eventually will decrease or eliminate the ceftazidime-induced *P. aeruginosa* resistance problems. Imipenem, if determined to be the main cause of an institution’s resistance problems, may be replaced by meropenem, which has not been associated with resistance. Formulary restriction is the only proven method of controlling resistance at the hospital and community level. The two most critical factors in antimicrobial prescribing at the millennium relate to the role of oral antibiotic therapy and an increasing awareness of pharmacoeconomic factors in antibiotic selection. Most nations have limited health care resources. Antimicrobial therapy constitutes a major portion of most hospitals’ drug expenditures. Using pharmacokinetic and pharmacodynamic...
principles to optimize antimicrobial dosing has helped reduce antibiotic costs. Clinicians can now maximize antibiotic therapy to assure optimal outcomes at minimal cost. The single most important and profound change in antimicrobial use at the millennium involves the increasing recognition that oral antibiotic therapy is equivalent to intravenous antibiotic therapy. Presently, there are sufficient oral antibiotics available, with excellent bioavailability, that provide the same blood and tissue levels as equivalent intravenous therapy. Because clinical outcome depends upon effective therapy, **regardless of route of administration**, oral therapy has important pharmacoeconomic implications and offers several important benefits to the patient and the institution. Antibiotics that lend themselves to IV to PO "switch programs" include doxycycline, minocycline, clindamycin, metronidazole, levofloxacin, chloramphenicol, TMP-SMX, acyclovir, fluconazole, intraconazole, and linezolid. These antibiotics have excellent bioavailability and are ideal for oral therapy alone or as part of IV to PO switch therapy regimens with the same efficacy as equivalent IV therapy. Most bacterial infectious diseases may be entirely treated by the oral route.

Oral antimicrobial therapy has profound pharmacoeconomic and infectious disease implications. Oral antimicrobial therapy is much less expensive than equivalent intravenous therapy. In addition, patients receiving oral antimicrobial therapy may be discharged from the hospital earlier, resulting in great savings in health care costs. Patients receiving oral antimicrobial therapy for most or all of their hospital stay obviously have few, if any, side effects related to intravenous therapy, e.g., chemical phlebitis, or IV-line infections. Previously, patients were admitted to hospital for intravenous antimicrobial therapy. Currently, unless a patient is critically ill or unable to take oral medications, intravenous therapy offers no advantage over well-chosen, equivalent, oral antimicrobial therapy for most infectious diseases. The clinician should not ask whether patients receiving the intravenous therapy should receive oral therapy. Rather, physicians should view all patients as candidates to receive oral therapy unless critically ill or unable to take oral medications. As the new millennium begins, the era of home intravenous therapy is ending, rendered obsolete by the increasing armamentarium of oral antibiotics that are equivalent to their intravenous counterparts.

In conclusion, antimicrobial therapy at the millennium has matured and evolved because experience has taught us several important lessons. Antibiotic side effects are becoming more important and are largely agent specific. Antimicrobial resistance potential is not related to volume, years of use, or class and is agent specific. Pharmacokinetics and pharmacodynamics have helped to optimize antibiotic dosing regimens. In the future, most antimicrobial therapy will be administered via the oral route. Clinicians should use the principles of antibiotic therapy that experience has taught us as a basis for continued progress in developing new antimicrobials and new applications. New uses have been found for old antibiotics; some provide effective therapy for emerging infectious diseases, e.g., doxycycline use in malaria, ehrlichiosis, Lyme disease, and nitrofurantoin or chloramphenicol may be used to treat VRE. Clinicians often find it difficult to evaluate promotional information to which they are subjected. In evaluating the potential usefulness of new antibiotics, clinicians must weigh their cost, resistance potential, side effect profile, and purported advantages against those currently available. New antibiotics, unless offering special advantage, should be introduced cautiously and be carefully observed for resistance problems or side effects during the first 2 years of general use. The critical factors for antimicrobial therapy to go beyond the millennium relate to achieving
optimal clinical outcomes while minimizing resistance potential problems and applying pharmacoeconomic considerations to antibiotic selection.

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