The drug therapy for diseases other than those caused by microbial agents involves treating the host. In infectious diseases therapy, the goal is to rid the host of the pathogen. Hence, drug therapy is aimed at the pathogen. Because a second living agent is involved in the triangle, drug therapy is affected by the pathogen’s nature, its tissue specificity, and, most importantly, the changes it undergoes to survive. The history of antimicrobial therapy has clearly demonstrated that the drugs that are used to treat infections are also responsible for making them more difficult to treat in the future. The only way to keep antimicrobial agents useful is to use them appropriately and judiciously.

The clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness. Clearly there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing. However, improved understanding of pharmacodynamic and pharmacokinetic parameters has greatly improved the use of antimicrobial agents. Most importantly, the integration of these pharmacodynamic and pharmacokinetic indices has greatly improved the correlation between in vitro susceptibility testing and in vivo clinical effectiveness and allows more realistic breakpoints. Finally, the clinical microbiology laboratory has advanced with improved methods to detect resistance as well as the adaptation of breakpoints that are more realistic.
New Uses for Older Antibiotics: Nitrofurantoin, Amikacin, Colistin, Polymyxin B, Doxycycline, and Minocycline Revisited
Burke A. Cunha

Nitrofurantoin, amikacin, colistin, polymyxin B, doxycycline, and minocycline are antibiotics with proven effectiveness against selected pathogens. These antibiotics have not developed resistance over time. As “low-resistance-potential antibiotics” that are effective against an increasing number of infections due to resistant gram-positive or gram-negative pathogens, these antimicrobials remain an important part of the antibiotic armamentarium. They will be used increasingly in the future, as highly resistant organisms continue to be important clinically and therapeutic options remain limited.

Macrolide and Ketolide Resistance with Streptococcus pneumoniae
Gary V. Doern

Antimicrobial agents in the macrolide family have long been considered drugs of potential utility in the management of infections caused by Streptococcus pneumoniae. However, with the emergence of macrolide resistance, the clinical value of macrolides in pneumococcal infections is threatened. In part, as a consequence of the development of macrolide resistance, recently the first agent in the ketolide antimicrobial class, telithromycin, was developed and introduced into clinical practice. The ketolides are macrolide antimicrobials whose chemistry has been modified so as to avoid the effects of the most common mechanisms of macrolide resistance with S pneumoniae. This discussion reviews the current state of resistance to macrolides and ketolides with S pneumoniae in North America.

Antibiotic Therapy for Helicobacter pylori
Jason Collins, Amira Ali-Ibrahim, and Duane T. Smoot

Helicobacter pylori is one of the most common bacterial infections in the world. H pylori infection of the gastric mucosa is the most common cause of peptic ulcers and is believed to be responsible for 50% to 60% of all gastric carcinomas. This infection is difficult to treat because the bacterium is located within the gastric lumen in the mucus and not within the gastric tissue. Antimicrobial therapy for H pylori includes two or three antibiotics plus either a proton pump inhibitor or a histamine receptor antagonist. H pylori readily develops resistance to antibiotics; therefore, if the initial treatment is unsuccessful, repeat treatment should include different antibiotics.

Antimicrobial Therapy of Clostridium difficile-Associated Diarrhea
Emilio Bouza, Almudena Burillo, and Patricia Muñoz

Clostridium difficile-associated diarrhea (CDAD) is the most common etiologically defined cause of hospital-acquired diarrhea.
Caused by the toxins of certain strains of *C. difficile*, CDAD represents a growing concern, with epidemic outbreaks in some hospitals where very aggressive and difficult-to-treat strains have recently been found. Incidence of CDAD varies ordinarily between 1 to 10 in every 1,000 admissions. Evidence shows that CDAD increases morbidity, lengths of stay, and costs. This article describes the clinical manifestations of CDAD, related risk factors, considerations for confirming CDAD, antimicrobial and nonantimicrobial treatment of CDAD, and issues related to relapses. The article concludes with a discussion of recent epidemic outbreaks involving CDAD.

**Antimicrobial Therapy of Multidrug-Resistant *Streptococcus pneumoniae*, Vancomycin-Resistant Enterococci, and Methicillin-Resistant *Staphylococcus aureus***  
Burke A. Cunha

Antibiotic resistance among pneumococci, enterococci, and staphylococci has become increasingly important in recent decades. Clinicians should be familiar with the nuances of antibiotic susceptibility testing and interpretation in selecting antibiotics for these infections. The clinical significance of penicillin-resistant *Streptococcus pneumoniae*, macrolide-resistant *S. pneumoniae*, and multidrug-resistant *S. pneumoniae* is discussed. The clinical spectrum and therapeutic approach to *Enterococcus faecalis* (ie, vancomycin-sensitive enterococci) and *E. faecium* (ie, vancomycin-resistant enterococci) are discussed. Differences in therapeutic approach between methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) infections are reviewed. Differences between in vitro susceptibility testing and in vivo effectiveness of antibiotics for hospital-acquired MRSA (HA-MRSA) are described. Lastly, the clinical features of infection and therapy of HA-MRSA and community-acquired MRSA (CA-MRSA) infections are compared.

**Monotherapy Versus Combination Therapy***  
Shilpa M. Patel and Louis D. Saravolatz

The science of antibiotic therapy for infectious diseases continues to evolve. In many instances where empiric coverage is necessary, treatment with more than one agent is considered prudent. If an etiology is identified, antibiotics are modified based on culture and susceptibility data. Even when the organism is known, more than one antibiotic may be needed. Decisions about antibiotics should be made after assessments of pertinent clinical information, laboratory and microbiology information, ease of administration, patient compliance, potential adverse effects, cost, and available evidence supporting various treatment options. Clinicians also need to consider synergy and local resistance patterns in selecting therapeutic options. In this article, the authors outline monotherapy and combination therapy options for several common infectious diseases.
Traditionally, antibiotics have been administered intravenously (IV) for serious systemic infections. As more potent oral antibiotics were introduced, and their pharmacokinetic aspects studied, orally administered antibiotics have been increasingly used for serious systemic infections was appreciated. Antibiotics ideal for oral administration are those that have the appropriate spectrum, high degree of activity against the presumed or known pathogen, and have good bioavailability. Oral antibiotics with high bioavailability, that is, ≥ 90% absorbed, achieve serum/tissue concentrations comparable to IV administered antibiotic at the same dose. The popularity of “IV to PO switch therapy” is possible because of the availability of many potent oral antibiotics with high bioavailability. Initial IV therapy is appropriate in patients who are in shock/ have impaired intestinal absorption, but after clinical defervesence, completion of therapy should be accomplished with oral antibiotics. As experience with “IV to PO switch therapy” has accumulated, confidence in oral antimicrobics for therapy of serious systemic infections has continued to increase. The trend in treating serious systemic infections entirely with oral antimicrobial therapy will continue, and is clearly the wave of the future.

Drug–drug interactions in the field of infectious diseases continue to expand as new drugs are approved, metabolic enzymes and transporters are identified, and recommendations for coadministration of drugs are revised. This article provides an overview of the principles and mechanisms of drug–drug interactions and describes pharmacokinetic-pharmacodynamic interactions commonly associated with antibacterial therapy, antiviral agents (nonretroviral), and drugs for tuberculosis.

Clinicians should be familiar with which antibiotics are safe to use for different types of penicillin-allergic reactions. Clinically, it is convenient to divide patients with penicillin allergy into three categories: those with unknown or possible reactions to penicillin, those with a drug fever or rash, and those with hives or anaphylactic reactions. β-lactam antibiotics may be used safely for patients with unknown/possible penicillin allergy and drug fever or rash. Penicillins or β-lactams should not be used for patients with hives or anaphylactic reactions. For all patients, clinicians should consider antimicrobial therapy with an antibiotic that does not cross-react with penicillins or β-lactams. This article reviews how clinicians should select antimicrobials in penicillin-allergic patients.
Clinical Approach to Antibiotic Failure
David Schlossberg

A systematic approach is presented for the patient with antibiotic failure. Noninfectious mimics of infection and nontreatable infections must first be excluded. Then, the clinician must identify those patients who have responded but have a surgical component of their infection or have complications separate from their initial infection. Such complications could include drug fever, phlebitis, decubiti, urinary tract infection, aspiration, and pulmonary embolism. Other patients may deteriorate clinically because of incorrect antibiotic coverage, failure of antibiotic to reach the site of infection, local inactivation of antibiotic, paradoxical response, immune compromise, or because they have reached the point of no return.

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