Management *of* Antimicrobials *in* Infectious Diseases

Impact of Antibiotic Resistance

Edited by

ARCH G. MAINOUS III, PhD

CLAIRE POMEROY, MD

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Dedication

To my son, Ryan W. Mainous

To my husband, William Preston Robertson

Preface

Management of Antimicrobials in Infectious Diseases: Impact of Antibiotic Resistance is designed to help clinicians who provide care for common infectious conditions. The book is intended as a resource for generalist physicians and midlevel practitioners as well as infectious disease specialists. Our goal is to delineate an understanding of commonly encountered infectious pathogens and outline rational approaches to the management of clinical entities encountered in both ambulatory and hospital-based practice.

The World Health Organization's recent 2000 Report on Infectious Diseases is focused on overcoming antimicrobial resistance and alerts us to the global importance of this issue. Optimal antimicrobial use is essential in this era of escalating antibiotic resistance, and an understanding of the appropriate use of antimicrobials, particularly in light of resistant pathogens, is necessary for clinicians engaged in frontline care.

Management of Antimicrobials in Infectious Diseases: Impact of Antibiotic Resistance was designed as a resource for the evidence-based antimicrobial treatment of infectious diseases encountered in both the hospital and outpatient settings. Special emphasis is placed on those aspects of treatment necessitated by the growing problem of antibiotic resistance.

Management of Antimicrobials in Infectious Diseases: Impact of Antibiotic Resistance opens with chapters focusing on the significant pathogens, followed by articles concentrating on their clinical management. This strategy was undertaken to provide the clinician with two different, yet complementary, ways of understanding and managing a clinical problem. In addition, in order to more fully explicate the message of appropriate use of antimicrobials, coverage is accorded to strategies for promoting such appropriate antimicrobial use and to future trends in both treatment and antimicrobial resistance.

It is our hope that *Management of Antimicrobials in Infectious Disease* will disseminate the practical knowledge every physician treating infectious diseases needs, both to improve the quality of medical care and to help address the rise of antimicrobial resistance.

Arch G. Mainous III, **PhD**
Claire Pomeroy, **MD**

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The Editors

Dr. Arch G. Mainous III is Associate Professor and Director of Research in the Department of Family Medicine at the Medical University of South Carolina. He is an accomplished investigator with research interests in improving the delivery of primary care and the overuse of antibiotics in respiratory infections. He has written more than 90 peer-reviewed articles in addition to three book chapters and a monograph on upper respiratory infections. Dr. Mainous' work on overuse of antibiotics has appeared in a variety of journals including *JAMA* and *Lancet.* His research has been honored by the American Academy of Family Physicians, the Society of Teachers of Family Medicine, and the North American Primary Care Research Group.

Dr. Claire Pomeroy is Professor and Chief of Infectious Diseases in the Department of Internal Medicine at the University of Kentucky. She also serves as Associate Chief of Staff for the Chandler Medical Center and Assistant Dean for Clinical Affairs at the University of Kentucky College of Medicine. Her research interests are focused on host response to infections, particularly opportunistic infections in immunocompromised patients. She has published extensively on a variety of topics related to infectious diseases and is the author of more than 70 peer-reviewed papers, as well as numerous book chapters.

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I
Introduction

1

Antibiotic Resistance and Implications for the Appropriate Use of Antimicrobial Agents

Andrea L. Benin and Scott F. Dowell

INTRODUCTION

The development of antibiotics completely revolutionized medicine in the second half of the 20th century. By 1940, the team researching penicillin recognized that its discovery was a monumental event. Fearing Hitler's invasion of Great Britain, they rubbed spores of *Penicillium notatum* into their coat linings to ensure that the mold would go with them in the event they had to escape rapidly *(1)*. In the more than 60 years since its discovery, penicillin has evolved from being a miraculous cure for infectious disease to being a small part of an arsenal of antimicrobial drugs. With the expansion of antibiotic therapy, hygiene, and sanitation in the United States, mortality due to infectious diseases has dropped markedly over the 20th century *(2–4)*. Since 1982, however, deaths attributable to infectious diseases have begun to climb *(3)* and this rise has occurred in parallel with increased antibiotic resistance.

Drug-resistant microorganisms are a growing global problem. Resistance develops in the environment of antimicrobial agent use and places both populations and individual patients at risk. Reducing the use of antimicrobial agents can decrease the spread of resistance; therefore judicious use of antibiotics must be part of the solution to drug resistance *(5–9)*. Here we discuss antimicrobial resistance mechanisms, their implications for clinical treatment, and ways to measure and monitor resistance. Because the factors promoting the spread of resistance and its optimal control measures differ for foodborne pathogens, hospital-acquired pathogens, and community-acquired pathogens, each of these groups is considered separately.

BACKGROUND AND EPIDEMIOLOGY OF RESISTANT PATHOGENS

Resistance among microorganisms is a predictable result of the Darwinian selective pressure of antimicrobial agents *(10)*. The first description of a mechanism for antibiotic resistance was published in 1940, when Abraham and Chain described an enzyme in *E. coli* that could hydrolyze penicillin *(11,12)*. Since then, the understanding of resistance at the molecular level has increased dramatically; unfortunately, at the same time, the number of pathogens exhibiting antimicrobial resistance has also increased dramatically. The public health impact of drug resistance derives from a combination of the magnitude of the resistance and its implications for morbidity and mortality.

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Magnitude of Antibiotic Resistance

Nearly all organisms have acquired resistance to some therapeutic agents; in some cases, the infections caused by resistant organisms create a significant public health burden (Table 1). To have public health importance these resistant organisms must cause substantially severe or frequent infections, be increasing in frequency, be managed with antimicrobial therapy as the standard of care, and be treatable by few alternative drugs.

An example of a bacterium that meets several of these criteria is resistant *Streptococcus pneumoniae.* In the United States alone, *S. pneumoniae* causes 3000 cases of meningitis, 50,000 cases of bacteremia, 125,000 hospitalizations for pneumonia, and 7,000,000 cases of otitis media per year. The case/fatality ratio may be higher than 25% for certain high-risk groups with bacteremia and meningitis despite appropriate treatment *(13,14).* Since its initial documentation in 1967 in Australia, pneumococcal resistance to penicillin has spread globally *(13);* in 1997 and 1998, population-based active surveillance for invasive *S. pneumoniae* disease in the United States showed that approx 25% of pneumococci are not susceptible to penicillin *(15,16).*

Chloroquine-resistant malaria represents another problem of public health importance on an international scale. Forty-one percent of the world's population live in a malarious area *(17).* Each year, 300–500 million cases of malaria occur, and nearly 3 million people die of malaria *(17–19).* Of 103 countries with reported malaria risk for travelers, 83 report widespread *Falciparum* resistance to chloroquine *(20).* In some regions, as many as 90% of the parasites may be resistant to chloroquine *(21).* The limited number of antimalarial drugs available and the long-term use of low-dose prophylactic therapy have been major factors in the development of parasite resistance to the available drugs *(22,23).*

Tuberculosis presents another resistance problem with broad public health ramifications. In 1997, nearly 20,000 cases of tuberculosis were diagnosed in the United States *(24).* Twelve percent of *Mycobacterium tuberculosis* strains in the United States are resistant to at least one drug *(25).* A large global survey conducted from 1994 to 1997 by the World Health Organization and the International Union Against Tuberculosis and Lung Disease documents that the problem is worldwide; resistant *Mycobacterium* was identified in 35 countries and regions. Of *M. tuberculosis* strains from patients with no prior tuberculosis treatment, 10% were resistant to at least one drug, and 1.4% were multidrug resistant; of strains from patients with previous tuberculosis treatment, 36% were resistant to at least one drug and 13% were multidrug resistant *(25).* In the United States, interventions targeting multidrug-resistant tuberculosis (MDR-TB) have begun to show success: MDR-TB declined from 2.8% to 1.1% of total tuberculosis cases from 1993 to 1998 *(26).*

Implications for Morbidity and Mortality

For some infections, resistance has been clearly associated with increased morbidity and mortality *(27).* In one study, only 65% of patients with pulmonary tuberculosis that was resistant to rifampin and isoniazid responded to alternative treatments and eventually had negative sputum cultures, compared with a 98–99% cure rate for drug-susceptible disease *(28).* Of patients with resistant infections resulting in treatment failure, 46% died *(28).* Likewise, human immunodeficiency virus (HIV) resistance to zidovudine predicts clinical progression of the acquired immunodeficiency syndrome (AIDS)

Table 1
Examples of Antimicrobial-Resistant Microorganisms of Public Health Importance

Microorganism	Mechanisms of Resistance	Percent Resistant in U.S.[a]	CDC Estimated Annual Resistant Infections in U.S.	References
Gram-positive bacteria				
Penicillin nonsusceptible *Streptococcus pneumoniae*[b]	Target alteration: PBP	25%	>490,000	*(15,45,52)*
Fluoroquinolone-resistant *Streptococcus pneumoniae*[c]	Target alteration: DNA gyrase and topoisomerase	0.5%	300	*(16)*
Vancomycin resistant *Enterococcus*[d] (nosocomial)	Target alteration: cell wall Bacterial regulatory system alteration	15% (non-ICU), 25% (ICU)	No estimate	*(82,104)*
Methicillin-resistant *Staphylococcus aureus* (nosocomial)	Target alteration: PBP	35% (non-ICU), 40% (ICU)	No estimate	*(45,82,105)*
Vancomycin intermediate *Staphylococcus aureus*[e]	Unknown	Few reported cases in world	<10	*(106)*
Gram-negative bacteria				
Fluoroquinolone-resistant *Neisseria gonorrhoeae*[f]	Target alteration: DNA gyrase and topoisomerase	0.1%	500–1000	*(107–110)*
Third-generation cephalosporin resistant *Klebsiella* (nosocomial)	Antibiotic modification: ESBLs	15% (non-ICU), 10% (ICU)	No estimate	*(52,82)*
Multidrug[g]-resistant *Salmonella typhi*	Antibiotic modification: β-lactamase (amp), acetylation (CAM) Target alteration: DHFR (TMP), dihydropteroate synthetase (SMZ)	12%	10–60[h]	*(45,51,111,112)*

(continues)

Table 1 (continued)

Microorganism	Mechanisms of Resistance	Percent Resistant in U.S.[a]	CDC Estimated Annual Resistant Infections in U.S.	References
Multidrug[i]-resistant nontyphoid *Salmonella*[j]	Multiresistance integrons	8%	112,000	*(55,56,113)*
Imipenem-resistant *Pseudomonas aeruginosa* (nosocomial)	Decreased permeability	10% (non-ICU), 15% (ICU)	No estimate	*(48,82,114,115)*
Acid-fast bacteria				
INH and rifampin resistant *Mycobacterium tuberculosis*	Target alteration or increased target production	1% no prior TB; 3% with prior TB	150	*(53)*[k]
Viruses				
Zidovudine[l] resistant human immunodeficiency virus	Target alteration: viral reverse transcriptase	1–2% in new cases	400–800[m]	*(65,116–119)*
Amantadine/rimantadine resistant influenza	Modified structural protein (M2 protein)	1%	No estimate	*(116,120)*
Acyclovir resistant herpes simplex virus[n]	Inhibition of drug activation: mutation in viral thymidine kinase Target alteration: viral DNA polymerase	5.3% (HIV positive); 0.2% (STD clinic)	No estimate	*(121,122)*
Fungi				
Azole-resistant *Candida* spp.	Increased drug efflux Target alteration: cytochrome P450 Increased target production Decreased cellular permeability	5–10% bloodstream; 10–20% mucocutaneous (HIV positive)	1000–2000	*(123–126)*[o]

Parasites				
Chloroquine resistant *Plasmodium falciparum*[p]	Increased drug efflux	Widespread worldwide—U.S. disease reflects region of importation.	No estimate	*(21,22,50)*

Abbreviations: PBP, penicillin binding protein; ICU, intensive care unit; tet, tetracycline; pen, penicillin; ESBL, extended spectrum β-lactamase; amp, ampicillin; CAM, chloramphenicol; TMP, trimethoprim; SMZ, sulfamethoxazole; DHFR, dihydrofolate reductase; INH, isoniazid; TB, tuberculosis.

Multidrug resistance is defined as resistance to three or more classes of antimicrobial drugs except in the case of *M. tuberculosis,* in which it is defined as resistance to INH and rifampin.

[a] Years vary between 1991 to 1999; *see* reference for exact year.

[b] Many are also multidrug resistant. Although not listed here, resistance to macrolides and fluoroquinolones is also important.

[c] Ofloxacin.

[d] Enterococci are intrinsically resistant to β-lactams, aminoglycosides, clindamycin, fluoroquinolones, and trimethoprim–sulfamethoxazole and readily acquire resistance to high concentrations of β-lactams, high concentrations of aminoglycosides, tetracycline, erythromycin, fluoroquinolones, rifampin, chloramphenicol, fusidic acid, nitrofurantoin, in addition to the glycopeptides vancomycin and teicoplanin.

[e] Although we have listed only vancomycin, these staphylococci are multidrug resistant.

[f] Although only fluoroquinolones are listed, quinolone resistant *N. gonorrhoeae* is also penicillin and tetracycline resistant.

[g] Ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole.

[h] Based on an estimated 100–600 cases per year *(111).*

[i] Ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline (linked resistance).

[j] Predominantly *Salmonella enterica* serotype Typhimurium phage type 104 (DT104).

[k] Centers for Disease Control and Prevention. Division of Tuberculosis Elimination. Unpublished data, 1998.

[l] Primary mutations associated with zidovudine and other nucleoside reverse transcriptase inhibitors.

[m] Based on an estimate of 40,000 new infections per year.

[n] Acyclovir requires activation by phosphorylation by viral enzymes-thymidine kinase in the case of herpes simplex. Cellular enzymes complete the phosphorylation. Then the drugs target viral DNA polymerase and prevent elongation of viral DNA by being preferentially incorporated into the elongating viral DNA chain thus terminating further viral DNA replication.

[o] Centers for Disease Control and Prevention. Division of Bacterial and Mycotic Diseases. Unpublished data, 1999.

[p] Chloroquine resistance in falciparum malaria is widespread; among countries with endemic *P. falciparum,* only Central America and Egypt have not reported resistance *(17).* Multidrug resistance is also a significant global problem *(17,22).*

and death *(29–31).* Pneumonia caused by *Streptococcus pneumoniae* that has high-level resistance to penicillin has been associated with increased mortality in some studies *(32,33),* and resistant pneumococcal meningitis has been associated with persistently infected spinal fluid *(34–36).* There is no typical relationship between antimicrobial resistance and virulence of the infecting organism; depending on the organism, resistant isolates may or may not be more virulent than their less resistant counterparts. However, because resistance can lead to treatment failure, resistant infections may result in more serious disease *(37).* For many organisms, evidence of increased mortality resulting from treatment with an ineffective or less effective drug is difficult to obtain because clinicians will either institute alternate empiric treatment based on knowledge of potential resistance or will change treatment based on lack of clinical response.

By 2000, there were few infections that were so resistant as to be practically untreatable. *Burkholderia cepacia* infections in patients with cystic fibrosis and vancomycin-resistant *Enterococcus* (VRE) in hospitalized patients may not be treatable with routinely available agents, but they affect a relatively small number of patients. For those illnesses that affect large numbers of people, such as malaria and AIDS, some treatment alternatives are often available, but expense or other considerations may make them impractical for most patients *(23).*

Because of the risk of excessive morbidity and mortality related to resistance, public health agencies and the medical community have reacted aggressively to the rising trends in antimicrobial resistance. Pharmaceutical companies have begun new drug investigations *(38–40);* researchers are developing new vaccines *(41);* the public health community has implemented enhanced surveillance *(3,4);* and educational initiatives for physicians, veterinarians, and the general public have stressed the importance of appropriate use of antimicrobial agents *(13,43,44,44a).*

CELL PHYSIOLOGY AND GENETICS OF ANTIMICROBIAL DRUG RESISTANCE

On the cellular level, antimicrobial resistance derives from changes in two interrelated processes: cellular physiology and genetic coding. Microorganisms use a number of physiological mechanisms, based on modifications of the organisms' normal molecular pathways, to resist killing by antimicrobial agents (Table 1). Each alteration in cellular physiology derives from a change in genetic encoding, and these gene coding changes come about in characteristic ways.

Cellular Physiologic Mechanisms

Three basic physiologic mechanisms cause most antimicrobial resistance: enzymatic modification of the antibiotic, alteration of antibiotic target sites, and changes in antibiotic uptake or efflux. Each organism may use one or more of these strategies (Table 1) *(12,45–47).*

A classic example of a bacterium that depends on antibiotic modification is *Staphylococcus aureus.* Since the 1950s *S. aureus* has been known to produce the enzyme β-lactamase. This enzyme cleaves β-lactam rings, resulting in inactivation of β-lactam-based antibiotics *(45,47).*

Resistance by target site alteration occurs when the antibiotic can reach its usual target but is unable to act because of a change in that target. For penicillin to act against streptococci, the drug depends on binding to the target penicillin-binding proteins (PBPs). Because penicillin-resistant *Streptococcus pneumoniae* produces a different PBP with low affinity for penicillin, it is able to evade the drug effects *(45,47).*

Bacteria can have decreased uptake of antibiotic as a result of reduced permeability of their outer layer. *Pseudomonas aeruginosa* and *Escherichia coli* have an outer membrane with low permeability to antibiotics *(48).* Because antibiotics must be able to penetrate the cell by means of bacterial porins, the diffusion rate of the drugs is altered by changes in these porin channels. Loss of the porin required for cellular entry of imipenem causes *P. aeruginosa* to develop imipenem resistance *(48).* Alternatively, cellular exiting of drug may be enhanced. Tetracycline resistance for a number of bacteria, including many enterobacteriaceae, some staphylococci, and some streptococci, results from active export of the antibiotic out of the bacterial cell (drug efflux) *(45,49).* Increased drug efflux is also a mechanism of chloroquine resistance in *Plasmodium falciparum (19,22,50).*

Genetic Basis for Resistance

The genetic changes leading to the cellular physiology of resistance are complex and varied, but there are three main types: chromosomal mutations of common resistance genes, acquisition of resistance genes carried on plasmids and other exchangeable genetic segments, and inducible expression of existing genes *(45,47,48,51,52).* Each type of genetic variation has implications on a population level for surveillance and on an individual patient level for clinical management (Table 2).

Chromosomal Mutations

Chromosomal mutations in common resistance genes can be spontaneous or can be complex, accumulated mutations (Table 2). For example, *Mycobacterium tuberculosis* acquires resistance when chromosomal mutations alter the bacterial antibiotic target site or cause the bacteria to overproduce the target *(53).* MDR-TB develops when mutations in individual chromosomal genes accumulate; the likelihood of a *M. tuberculosis* mutant being simultaneously resistant to two or more drugs is the product of individual probabilities of a single mutation *(53).* Thus for the purposes of surveillance for antimicrobial resistance, organisms such as *M. tuberculosis* will gradually change their susceptibility patterns, and the development of resistance to each drug is independent of the existing drug resistances (Table 2).

Chromosomal mutations hold implications for clinicians choosing treatment for individual patients. Clinicians can expect microorganisms that typically acquire chromosomal mutations to have stable resistance patterns in the short term; yet, selective pressures in an individual patient will be very important over the long term. This relative stability means that clinicians can test for resistance in a specific microorganism and tailor antimicrobial therapy accordingly (Table 2). Because the probability of a multiply resistant organism developing in one patient is the product of the probabilities of developing each resistance individually, a high load of the organism in the infected person is needed for multiple resistance to develop, and treatment with multiple drugs may prevent the emergence of resistance *(53).*

Table 2
Genetic Mechanisms of Antimicrobial Resistance with Public Health and Clinical Implications

Genetic Changes	Examples of Pathogens	Surveillance Implications	Clinical Implications
Chromosomal mutations—accumulated and single mutations	*Mycobacterium tuberculosis* HIV, *Plasmodium falciparum*	Nonsusceptibility prevalence will change gradually, independent of other drug resistances	Can test for specific drug and microorganism combinations, expect stability of susceptibility over short term, selective pressure over time in an individual patient is important
Plasmid and other gene segments which are exchanged among microorganisms (transposons, integrons, phage genes)	*Klebsiella* (extended-spectrum β-lactamases)	Nonsusceptibility prevalence can change suddenly, often with several drug resistances linked together	Anticipate co-resistance
Inducible expression	Influenza, *Enterobacter,* HIV, vancomycin resistant *Enterococcus*	Surveillance is not useful because resistance develops during therapy	Anticipate mid-treatment failure despite initial susceptibility of isolate

Plasmids and Exchangeable Gene Segments

Plasmids and other exchangeable segments of genes such as transposons, gene cassettes, integrons, and phage genes are more rapidly disseminated than are chromosomal mutations. Transposons are segments of DNA that have a repeat of an insertion sequence element at each end and can migrate from one plasmid to another within the same bacterium, to a bacterial chromosome, or to a bacteriophage. Gene cassettes are a family of discrete mobile genetic elements that each contain an antibiotic resistance gene and are dependent upon integrons for integration in chromosomes *(54).* Integrons are receptor elements on the chromosome that provide the site into which the gene cassette is integrated and provide the enzyme for integration *(54).*

One example of the role of these exchangeable gene segments is the plasmid encoded, extended-spectrum β-lactamases (ESBLs) in Gram-negative organisms. The ESBLs confer resistance to ampicillin, carbenicillin, ticarcillin, and the extended-spectrum cephalosporins. Their broad activity arises from amino acid substitutions that

alter the configuration around the active site of the β-lactamase enzyme and thus increase the enzyme affinity for broad-spectrum β-lactam antibiotics *(45)*.

The rapid exchangeability of plasmids or other exchangeable gene segments has several implications: (1) surveillance systems need to detect sudden changes in resistance patterns in a community, (2) resistances may be easily transferred between bacterial species, and (3) resistances to several different drugs may travel together. For the clinician treating an individual patient, it is important to expect resistance to multiple drugs when resistance to one drug occurs. This co-resistance problem should always be anticipated, particularly when one resistance is known to be carried on an exchangeable element (Table 2). In 1998, 32% of *Salmonella* isolates in the United States demonstrated a linked five-drug resistance pattern, in contrast to fewer than 1% in 1979–1980 *(55,56)*. This five-drug resistance pattern is based on exchangeable gene segments, and occurs in *Salmonella enterica* serotype Typhimurium definitive type (DT)104, a widespread pathogen in the United States and the United Kingdom and one associated with antimicrobial agent use in farm animals *(56,57)*. Of *S. pneumoniae* isolates that are resistant to penicillin, two-thirds are also resistant to crythromyom and 93% are nonsusceptible to trimethoprim-sulfamethoxazole (57a) (CDC, unpublished data, 1998). Although *S. pneumoniae* co-resistances are not plasmidborne, they are complex gene mosaics that appear to be tightly linked like those on plasmids.

Inducible Mechanisms

Inducible mechanisms cause resistance that arises during treatment with a given antimicrobial agent. For example, treatment of influenza A with rimantadine regularly results in the rapid emergence of resistant virus in the affected patient *(58,59)*. Also, several Enterobacteriaceae possess a cephalosporinase that is not normally expressed, but certain cephalosporins will trigger expression of high concentrations of the enzyme *(60)*. Effective surveillance for these inducible mechanisms is not possible because they are not expressed phenotypically at baseline. For pathogens known to have inducible mechanisms of resistance, the clinician must be prepared for mid-treatment failure despite initial sensitivity of the isolate.

MEASURING ANTIBIOTIC RESISTANCE

Laboratory Testing

Laboratory testing for antibiotic resistance is generally done by using phenotypic assays, although for an increasing number of cases, genotype-based assays can provide rapid information *(61,62)*.

Phenotypic assays are based on in vitro inhibition of growth of a microorganism in the presence of an antibiotic. These assays are used for organisms that can be cultured on artificial media—bacteria on agar or broth media and viruses in cell culture. For bacteria, disk diffusion or broth/agar dilution methods are used to determine the minimum inhibitory concentration (MIC) *(61,62)*. The MIC is the minimum concentration of antibiotic that will inhibit growth of the organism in vitro. For viruses, drug susceptibility is expressed as the drug concentration that is required to inhibit viral replication by 50% (IC_{50}) *(63,64)*.

Genotypic assays test for the presence of resistance genes that confer phenotypic resistance. Although they are indirect, genotypic analyses are important for organisms

that are difficult to grow in culture; many viruses, such as hepatitis B, cannot be cultivated at present. Genotypic assays are particularly advantageous for viruses because in comparison to viral culture, which can take a week or more, many genotypic tests are relatively quick to perform *(63).* Types of assays include sequencing of the microorganism's genome, restriction fragment length polymorphism assays, and line probe assays *(63,65).*

Whereas phenotypic testing by disk diffusion for common bacterial resistance requires little technology and resources, many of the other resistance testing techniques are complex. A laboratory may be constrained by the limits of technological resources available and also by the limits of testing technology.

In the United States, the National Committee for Clinical Laboratory Standards (NCCLS) defines antimicrobial susceptibility for most pathogens of clinical interest. Resistant isolates are those organisms that are not inhibited by the usually achievable concentrations of antimicrobials. Intermediate resistant isolates are those organisms with MICs that approach typically attainable blood and tissue concentrations of antimicrobial drugs and for which response rates may be lower than for susceptible isolates. Susceptible isolates are those organisms for which an infection due to the pathogen may be appropriately treated with the usual dosage of the antimicrobial drug *(66).* Nonsusceptible refers to the combined categories of full and intermediate resistance.

For MICs to be meaningfully interpreted, NCCLS takes into account multiple factors when defining the breakpoints for susceptibility for a given antimicrobial agent. These factors include in vitro activity, pharmacokinetics, achievable tissue concentrations, approved indications and doses, and available clinical data *(61,67).*

Conceptually, results of susceptibility testing are divided into biological and clinical resistance categories. The MIC represents the biological resistance and documents in vitro behavior of an organism. Biological resistance does not necessarily translate into clinical resistance; clinical resistance implies an association with in vivo treatment failure. Even though in most situations in vitro drug resistance testing correlates with clinical treatment outcome, organisms that may be classified as nonsusceptible to a specific antimicrobial agent by MIC testing may still be treatable clinically with that agent and vice versa. For example, in one study only 8% of *P. falciparum* in parts of Kenya demonstrated in vitro chloroquine resistance; yet more than 50% of infected persons had clinical treatment failure during controlled in vivo resistance testing *(19).* Because treatment failure can be the result of many factors in addition to drug resistance, such as host immunity, proper diagnosis, drug absorption, and dosing compliance, clinicians must distinguish between clinical treatment failure and true drug resistance *(19).*

Surveillance

By measuring and tracking resistance on a population level, surveillance is an essential component in the understanding and control of resistance. Surveillance has been defined as "a continuous and systematic process of collection, analysis, interpretation, and dissemination of descriptive information for monitoring health problems" *(68).* Surveillance systems consist of networks of persons carrying out activities on many levels from local to international.

Classically, surveillance has been described as either active or passive. With an active surveillance system, the organization conducting the surveillance initiates the

procedure to obtain reports, such as regular telephone calls or visits to laboratories. Passive surveillance relies on clinicians or laboratories to contact the organization doing the surveillance. Because there are many different permutations of active and passive surveillance, before applying surveillance data to a given population, the clinician or public health practitioner must understand the source of the data and the type of surveillance system *(68).* Notifiable disease reporting, laboratory-based surveillance systems, and clinics with internal tracking systems may all obtain information about antibiotic resistance; but because the methods of data collection differ, estimates of resistance often differ as well. No matter where surveillance data come from whether population based systems or nonsystematic clinic samples, they can be difficult to use for guidance of treatment choices for individual patients. An individual patient may or may not be appropriately represented by a surveillance population, and resistance may vary widely depending on how it is measured, as well as by region and by facility within a region *(15).*

At local levels, hospitals generally keep records of the resistance patterns present in the isolates that are recovered in their laboratories, and at state levels many public health departments track the prevalence of certain resistant isolates in their state. On the national level in the United States, the Centers for Disease Control and Prevention (CDC) has several active surveillance systems that collect population-based resistance data from laboratories around the country for certain bacteria. For example since 1989, CDC's Active Bacterial Core Surveillance system (ABCs) has collected data for all invasive isolates of selected bacteria, including *Streptococcus pneumoniae,* from carefully defined populations *(16).*

Heightened surveillance for a particular outcome can be useful for public health goals and for good patient care. Only a handful of glycopeptide (vancomycin) intermediate *Staphylococcus aureus* (GISA) infections have occurred throughout the world. Because of the severity of disease with GISA, the lack of available treatment options, and the potential for the emergence of a fully resistant strain, guidelines for heightened passive surveillance were developed. These guidelines encourage enhanced reporting for GISA infections so that they can be identified rapidly, interventions can occur, and risk factors for infection can be determined *(12,69).*

There are many barriers to population-based surveillance and the appropriate use of the resulting data *(70).* At the most basic level, the laboratory performing the initial isolation must have adequate resources and measurement capacity, and laboratories in a given surveillance area must be standardized and able to communicate. When well constructed population-based active surveillance although expensive, has the potential to provide accurate, representative, and timely information on changing rates and patterns of resistance.

FACTORS PROMOTING ANTIMICROBIAL RESISTANCE AND MEASURES TO CONTROL ITS SPREAD

Antibiotic exposure is the main factor promoting antibiotic resistance in both populations and individuals, although crowding and other risk factors also contribute selective pressure for resistance and encourage its spread (Table 3) *(8,12,71,72).* We have categorized resistant pathogens as foodborne, hospital-acquired, or community-acquired. While appropriate measures to curb development of resistance have different

Table 3
Three Types of Resistant Pathogens and the Implications for Control Measures

	Foodborne	Hospital-Acquired	Community-Acquired
Definition:	Resistant pathogen acquired from food ingestion	Resistant pathogen acquired in hospital	Resistant pathogen acquired in the community
Example:	Fluoroquinolone-resistant *Campylobacter*	Vancomycin resistant *Enterococcus*	Drug-resistant *Streptococcus pneumoniae*
Factors associated with increased likelihood of resistance:	Antibiotics in feed, therapeutic antibiotics, animal hygiene, structural confines on farms	Parenteral antibiotics, prolonged antibiotics, empirical antibiotic therapy, surgical prophylaxis, poor staff infection control practices	Recent (previous 3 mo) antibiotic use, community with high resistance rates, day care, schools, military
Audience for education:	Veterinarians, regulatory agencies, farmers	Hospital personnel	Community medical practitioners, public
Control measures:	Decreased antibiotics in animal feed, irradiation of food	Formulary controls, good infection control precautions (hand-washing), cohorting, laboratory surveillance for resistance	Appropriate antibiotic use by clinicians, public education, improved diagnostic techniques, vaccines

nuances for each pathogen category, they all rely on improvement in the appropriate use of antimicrobial agents.

Foodborne Pathogens

Factors that Promote Resistance in Foodborne Pathogens

Foodborne pathogens are those that cause illness when a person ingests contaminated meat or other food product. Animals are regularly exposed to antibiotics, as half of the antibiotics used around the world are used in animals *(73).* Every time an animal is exposed to an antimicrobial agent, the animal's bacterial flora have the opportunity to develop resistance. Thus food animals harbor resistant pathogens and pass these pathogens to consumers; examples include *Salmonella, Campylobacter, Enterococcus,* and *Escherichia coli* strains *(42,74).*

A primary source of animal exposure to antibiotics occurs from animal feed: because of their growth promotion effects, antibiotics are routinely added to animal

feed around the world *(62,74,75).* Millions of tons of antibiotic are used in animal feed yearly and these antibiotics provide a constant low level of antibiotic exposure and promote development of resistance *(62).* Animals are also exposed to antibiotics for treatment and prophylaxis of infection *(74,76).* Restrictions on veterinary antibiotic use are variable; in many areas, veterinary use is unregulated and antibiotics are sold by animal supply stores without requiring a prescription. Antibiotic use is not the only factor in the development and spread of resistance; specific animal husbandry practices are also important. When animals are crowded together or farming hygiene is poor, the opportunity for spread of resistant microorganisms is increased.

Control of Foodborne Pathogens

The key measures to control resistance and its transmission in foodborne pathogens are discontinuation of the use of antibiotics for additives for growth promotion and the removal of contaminating pathogens with means such as irradiation. In the United States, the use of antibiotics for growth promotion is still widespread, but in some countries, antibiotics that are used for human therapy are prohibited for use as growth promoters in animals *(76,77).* The United States Food and Drug Administration (FDA) has recently begun to actively encourage judicious use of antibiotics for veterinary therapeutic purposes and to undertake antimicrobial regulatory activities *(44,44a).* Adequate regulatory intervention will be critical to reduce not only the threat of resistance due to therapeutic drug use but also the threat caused by feed additives. Other strategies to control resistance in foodborne pathogens include educating animal farmers about antibiotic practices, vaccinating animals, and enhancing practices for animal hygiene *(74,76).* Increased surveillance to measure antimicrobial consumption by food animals and development of resistance may heighten awareness and provide the necessary data to enable the implementation of interventions *(44,44a,74).*

Measures such as pasteurization, irradiation, careful food preparation, and effective cooking can work to limit transmission of resistant bacteria between animals and humans *(73,78,79).* Encouraging general use of these measures to reduce transmission of foodborne pathogens is a central goal of both state level and nationwide public health campaigns; their consistent implementation can decrease the spread of all foodborne pathogens, both susceptible and resistant.

Hospital-Acquired Pathogens

Factors in Development of Hospital-Acquired Pathogens

In the dense microcosm of the hospital, antibiotics are frequently used and bacteria may be readily passed from one patient to the next *(46,80–82).* Antibiotic resistance develops in response to the heavy use of antimicrobial agents in hospitals, and resistance to many drugs has been closely correlated with previous use of that drug. One particular concern is patients who have had exposure to vancomycin and thus are more apt to develop infections with vancomycin-resistant *Enterococcus* (VRE) *(42).* Once the selective pressure of antibiotic exposure causes susceptible hospital-acquired pathogens to become resistant, these pathogens cause secondary infections when spread further in the hospital. Spread occurs because patients in hospitals are in close proximity to each other, and there are many opportunities for the exchange of infecting organisms. Exchange can be by means of respiratory droplets, the hands of healthcare personnel and visitors, and equipment that has been insufficiently cleaned *(83,84).*

Control of Hospital-Acquired Resistance

The key measures for control of resistance in hospital-acquired pathogens are reduction in antimicrobial use, formulary restrictions, and good hand-washing practices. Hospital-acquired resistance must be controlled both by preventing the development of resistance in individual patients with previously susceptible infections and also by controlling the spread of nosocomial pathogens that have already acquired antimicrobial resistance traits *(46).*

The judicious use of antibiotics in the hospital setting can slow the development of resistant pathogens. Formulary restrictions have been one way to successfully decrease inappropriate hospital use of antibiotics *(7,46).* Another way to facilitate treatment with the most appropriate and narrowest spectrum antimicrobial drug is by the use of rapid, sensitive, and specific diagnostic tests. In addition, clinicians should base empiric treatment of hospitalized patients with probable nosocomial infections on hospital surveillance antibiograms. Because hospitals will have complete information for nosocomial pathogens, the hospital antibiogram is particularly well suited for use in deciding empiric treatment for nosocomial infections. Control of the transmission of hospital-acquired resistant pathogens requires consistent use of infection control practices such as hand-washing, gowning, gloving, and use of isolation rooms *(82,84).*

Infection control guidelines such as those created jointly by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America address the problems of antibiotic choice, infection control practices, and surveillance systems in the hospital setting *(46).* In areas and countries where antibiotic availability and hospital resources are limited, changes in hospital practices will be more difficult to implement than in areas where resources are relatively abundant.

Hospital-based health care professionals should be educated about the appropriate uses of antibiotics, infection control practices, resistance testing, and surveillance data. However, educational interventions can be a challenging way to induce behavior change. Constraints on time and persistent acceptance of long-held beliefs are difficult obstacles for any educational program to overcome *(85).*

Community-Acquired Pathogens

Factors in Development of Resistance in Community-Acquired Pathogens

Exposure to antibiotics also promotes antimicrobial resistance among pathogens acquired in the community. One example is drug-resistant *Streptococcus pneumoniae* (DRSP) *(9). S. pneumoniae* is a frequent cause of outpatient respiratory infections including otitis media, pneumonia, and sinusitis. The strongest risk for developing an infection with DRSP is the prior use of antibiotics, in particular during the 3 previous months *(86,87).* Other risk factors for DRSP infection relate either directly or indirectly to antibiotic exposure. These risk factors have included young age, white race, higher income, suburban residence, and day care attendance *(86,88–91).* Day care attendance has been an important risk factor, probably because the environment presents a combination of frequent antibiotic usage with crowding and close contact of a large number of small children who share respiratory and other secretions *(92–95).*

Control of Resistance in Community-Acquired Pathogens

The key measure for controlling antibiotic resistance in community-acquired pathogens is avoiding the use of antibiotics for probable viral conditions *(43,96).* However, other measures—education, vaccinations, surveillance, and the development of new antimicrobial agents—supplement judicious antibiotic use, and are actively being pursued by public health advocates, pharmaceutical companies, and researchers.

Although time-consuming and labor-intensive, education can result in decreased antibiotic use *(5,8,97)* and subsequently decreased community-acquired resistance *(5,8).* To decrease overprescribing, education of health care professionals should emphasize judicious antibiotic use and the issues of resistance in their community. Educating the public about the need for prudent use of antimicrobial agents will raise awareness of resistance issues and enable patients and their families to cooperate with their healthcare providers and seek care appropriately.

Vaccination can prevent disease caused by community-acquired pathogens and, in some cases, may play a role in decreasing resistant pathogens. The current conjugate 7-valent pneumococcal vaccine formulation covers more than 75% of resistant pneumococci and reduces carriage. Routine use of this conjugate pneumococcal vaccine to prevent pediatric disease may prove to be a valuable tool in controlling pneumococcal resistance *(41).*

Surveillance has an important role in describing the resistance problem and suggesting new management possibilities *(5,8,96).* However, because of the variation in populations and the importance and difficulty of compiling surveillance data that is population-based and relevant to a particular locale, it may be inappropriate to use surveillance information to directly guide outpatient management *(71).* For community-acquired infections, appropriate culture and susceptibility information is not often available for the most common outpatient illnesses such as otitis media. For this reason, on a local level in an outpatient setting, the application of hospital-based antibiograms is uncertain. The difficulty of creating a truly representative surveillance system for resistance in community-acquired pathogens combined with the financial cost of surveillance on a scale large enough to represent common outpatient infections present an enormous challenge to the development of useful outpatient population-based surveillance.

Emerging resistance continues to drive the need for development of new antibiotics. Several new classes of antibiotics, including the oxazolidinones, streptogramins, fluoroquinolones, and others, hold promise for treating resistant infections such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus (98).*

Fundamentally, however, to decrease resistance, the selective pressure of antibiotic use must decrease. In 1992, some 110 million prescriptions for oral antimicrobial drugs were written in the United States, three-quarters of which were for upper respiratory tract infections *(99).* Most of these prescriptions were for viral infections and therefore unnecessary *(99–101).* Because upper respiratory tract infections represent such a large amount of unnecessary antibiotic use and because antibiotic use in the recent past is associated with carriage of resistant pneumococci *(87)* and invasive disease *(86,87),* efforts to decrease antimicrobial resistance have focused on judicious use of antimicrobial agents for outpatient upper respiratory tract infections *(43,87,102).*

In some areas and countries, judicious antibiotic use may be hindered both by limitations of antimicrobial agent availability and also by the ability to buy antibiotics

without a prescription. Although freely available over the counter in some parts of the world, antimicrobial agents are costly, and some evidence indicates that in most cases people will consult with a healthcare provider before purchasing them. In one study on the outskirts of Mexico City, 72% of antibiotic courses sold had been recommended by a physician despite the widespread availability of drugs without a prescription *(103)*.

In 1998, the CDC with the American Academy of Pediatrics published the "Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections" to address the issues of treatment of upper respiratory infections in the era of antimicrobial resistance *(43)*. These principles identify specific conditions for which antibiotics should be used and where they should be avoided; they may be helpful to practitioners by providing an up-to-date review of the literature and expert discussion of the issues. However, guidelines cannot substitute for critical thinking on the part of the practitioner, and physicians are the key contact for successful antibiotic control programs.

CONCLUSION

Antimicrobial resistance is widespread and growing in scope. Understanding the specific resistance mechanism present in a particular pathogen can help clinicians manage individual patients and can help public health practitioners conduct appropriate surveillance of populations. Few resistant infections are completely untreatable in 2000, but many are associated with increased morbidity and mortality. Efforts to decrease inappropriate use of antimicrobial agents, decreasing the antimicrobial pressure that drives natural selection for resistance, hold promise for prolonging the lifespan of currently available antimicrobial agents. The main measures to control resistance depend on the type of pathogen. The key measures for foodborne pathogens are irradiation and reducing antibiotics in animal feed; for nosocomial pathogens, formulary controls and infection control programs; and for community-acquired pathogens, promoting appropriate use of antibiotics for upper respiratory tract infections.

Key Points

- Antimicrobial resistance is widespread and growing in scope; many resistant infections are associated with increased morbidity and mortality.
- Understanding the specific resistance mechanism present in a particular pathogen can help clinicians manage individual patients and can help public health practitioners conduct appropriate surveillance of populations.
- Reduction in the inappropriate use of antimicrobial agents is essential to prolong the lifespan of currently available antimicrobial agents.
- The main measures to control resistance depend on the mode of transmission of the resistant pathogen. The key measures for foodborne pathogens are irradiation and reducing antibiotics in animal feed; for nosocomial pathogens, formulary controls and infection control programs; and for community-acquired pathogens, promoting appropriate use of antibiotics for upper respiratory tract infections.

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II
Significant Pathogens

2
Gram-Positive Bacteria

Thomas S. Stalder and Laurel C. Preheim

STREPTOCOCCUS PNEUMONIAE

The pneumococcus *Streptococcus pneumoniae* commonly grows in pairs (diplococci) but also can grow in short chains. An outer polysaccharide capsule protects the organism against phagocytosis, and pneumococcal virulence is related to the composition and size of the capsule *(1)*. There are 90 known capsular types. Anticapsular antibodies induced by infection or vaccination are protective in normal hosts. The pneumococcal cell wall lies directly beneath the capsule and is composed of murein and glycopeptides. Cell wall antigens are responsible for the intense inflammatory reaction associated with pneumococcal infections. Cell wall components also facilitate pneumococcal attachment to and entry into activated host cells. The phosphorylcholine moiety of lipoteichoic acid structurally mimics platelet-activating factor (PAF). This allows pneumococci to subvert and attach to PAF receptors on cell surfaces *(2)*. Pneumolysin is another important virulence factor produced by virtually all pneumococcal clinical isolates. A potent cytotoxin, pneumolysin injures neutrophils, endothelial cells, and alveolar epithelial cells *(3)*.

Penicillin resistance in pneumococci is due to alterations in penicillin-binding proteins (PBPs), enzymes that are involved in synthesis and modification of bacterial cell walls. Although the definition of penicillin resistance has varied, *S. pneumoniae* is defined as penicillin susceptible when the minimum inhibitory concentration (MIC) is ≤ 0.06 μg/mL. Resistance is intermediate when the MIC is 0.1–1.0 μg/mL and high when the MIC is ≥ 2.0 μg/mL *(4)*. These breakpoints are based primarily on clinical outcome data for pneumococcal meningitis.

Clinical infections caused by penicillin-resistant *S. pneumoniae* were first reported in the late 1960s. Ten years later pneumococci highly resistant to penicillin (MIC 4–8 μg/mL) were isolated in South Africa, and strains that were resistant to three or more classes of antimicrobial agents were identified. The incidence and prevalence of drug-resistant *S. pneumoniae* continued to increase worldwide and became a global concern by the 1990s (reviewed in ref. *5*). In 1997 Doern et al. studied respiratory isolates of *S. pneumoniae* from 27 United States medical centers and seven Canadian institutions. Among the 845 U.S. isolates, only 56.2% were susceptible to penicillin. The percentages of penicillin-intermediate strains and strains with high-level resistance to penicillin were 27.8% and 16%, respectively *(6)*.

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An increasing number of pneumococcal isolates are demonstrating resistance not only to penicillin but to other antimicrobial agents as well. Most β-lactam antibiotics bind to the same or closely related pneumococcal PBPs. Thus mutations resulting in decreased affinity of penicillin to PBPs can be associated with cross-resistance to penicillin cogeners, cephalosporins, and β-lactam–β-lactamase inhibitor combinations. Because not all β-lactam antibiotics bind to the same PBPs or bind with the same affinity, certain β-lactams retain activity against most penicillin-resistant pneumococci. These agents include the extended-spectrum third-generation cephalosporins, cefotaxime and ceftriaxone, and the carbapenems, imipenem/cilastin and meropenem. Pneumococcal resistance to non-β-lactams such as the macrolides, tetracyclines, chloramphenicol, fluoroquinolones, and trimethoprim–sulfamethoxazole also is being reported with increasing frequency *(5,6).*

Antibiotic-resistant *S. pneumoniae* appears to be no less virulent than antibiotic-susceptible pneumococcal strains and causes the same clinical infections. Sinusitis and otitis media are the most common infections caused by this organism. Although its etiological significance in acute bronchitis is unclear, *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia. Bacteremia occurs in approx 20% of adults with pneumococcal pneumonia, and pneumococcal bacteremia without a source is a relatively common invasive bacterial infection in children. *S. pneumoniae* is the most common cause of bacterial meningitis in adults and children. Less commonly reported infections due to *S. pneumoniae* have included septic arthritis, peritonitis, orbital cellulitis, osteomyelitis, epiglottitis, and endocarditis.

Certain populations are at increased risk of colonization by and thus infection from drug-resistant *S. pneumoniae.* Among children, day care attendance and frequent exposure to antibiotic therapy are risk factors. For adults, risk factors for carriage of resistant strains include old age; coexisting illness or underlying disease; immunodeficiency; HIV infection; recent antibiotic therapy; family member of children who attend day care; or institutionalization in a nursing home, hospital, or prison *(5).*

Because the optimal management of infections caused by antibiotic-resistant *S. pneumoniae* remains undefined, there is no general agreement among experts. Current treatment strategies are based upon the results of in vitro susceptibility studies, animal models, case reports, and series of cases. The reader is referred to several comprehensive reviews for details on this subject *(5,7,8).*

Meningitis (Table 1)

Penicillin, even in high doses, does not achieve adequate cerebrospinal fluid (CSF) concentrations to adequately treat meningitis caused by pneumococci that have an MIC to penicillin of ≥ 0.1 μg/mL. More recently chloramphenicol also has been found to be an unreliable substitute for penicillin in this setting. Therapy with cefotaxime or ceftriaxone has been widespread and largely successful. However, the past decade saw increasing reports of treatment failures associated with these third-generation cephalosporins in patients with pneumococcal meningitis. In most cases the ceftriaxone or cefotaxime MIC was ≥ 2.0 μg/mL, but several failures were reported with MICs ≤ 0.1 μg/mL. High doses of cefotaxime (300 mg/kg/d to a maximum of 24 g) have been used successfully in cases with MICs of 1.0–2.0 μg/mL. Studies in a rabbit model

Table 1
Treatment Strategies for Meningitis Caused by Antibiotic-Resistant *S. pneumoniae*[a]

Penicillin MIC (μg/mL)	Dosage Cefotaxime/ Ceftriaxone MIC (μg/mL)	Therapy[b]	Children[c]	Adults
≥0.1	≤0.5	Cefotaxime or ceftriaxone	200–225 mg every 6 or 8 h 100 mg every 12 or 24 h	2 g every 6 h 2 g every 12 h
	1.0	Cefotaxime or	300 mg every 6 or 8 h	300 mg[c] every 6 or 8 h (up to 24 g total)
		ceftriaxone plus vancomycin	100 mg every 12 or 24 h 60 mg every 6 h	2 g every 12 h 60 mg[c] every 6 h (up to 2 g total)
	≥ 2.0	Same as for 1.0 μg/mL		
		Plus rifampin	20 mg every 12 h (up to 600 mg total)	300 mg every 12 h

[a] Adapted from ref. *(8)*.
[b] Fair research-based evidence, with substantial expert opinion.
[c] Doses are given as amounts per kilogram per day.

demonstrated that a combination of vancomycin plus ceftriaxone was superior to vancomycin alone for treatment of meningitis caused by a pneumococcal strain resistant to cefotaxime (MIC 2–4 μg/mL). Furthermore, the administration of dexamethasone before antibiotics decreased the concentrations of vancomycin and ceftriaxone but not rifampin in CSF. Dexamethasone does not appear to decrease the penetration of vancomycin or ceftriaxone into CSF in children, although it may alter vancomycin penetration in adults.

The use of dexamethasone in addition to antibiotics for the treatment of pneumococcal meningitis is controversial. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that dexamethasone be considered for treatment in infants and children *(9)*. Data supporting the use of dexamethasone in adults with pneumococcal meningitis are even less convincing *(10)*.

Pneumonia

Numerous studies on the antibiotic treatment of pneumococcal pneumonia in children and adults have failed to show a correlation between clinical outcome and infection with penicillin-resistant strains. Pallares et al. studied 504 adults with severe pneumococcal pneumonia from 1984 to 1993 *(11)*. When predictors of mortality (age ≥ 70 yr, serious underlying disease, heart failure, shock, multilobar pneumonia, leukopenia, nosocomial pneumonia, and polymicrobial pneumonia) were considered, there was no significant difference in mortality between those infected with penicillin-susceptible or penicillin-resistant pneumococci. Among patients who were treated with cefotaxime

or ceftriaxone, mortality rates were similar for those infected with cephalosporin-susceptible (24%, $n = 168$) and those with nonsusceptible (22%, $n = 18$) strains. Guidelines for the treatment of adult pneumonia published by the Infectious Diseases Society of America *(12)* recommend the use of parenteral penicillin G or oral amoxicillin as preferred agents for penicillin-susceptible pneumococci. For strains with intermediate susceptibility (MIC 0.1–1 μg/mL), parenteral penicillin G, amoxicillin, ceftriaxone, cefotaxime, fluoroquinolones (levofloxacin, moxifloxacin, or gatifloxacin), or other agents based on in vitro susceptibility test results are preferred. Clindamycin, doxycycline, and oral cephalosporins (cefpodoxime, cefprozil, cefuroxime) are alternative antimicrobials. For highly resistant strains (MIC ≥ 2.0 μg/mL) a fluoroquinolone, vancomycin, or other agents based on in vitro susceptibility test results are preferred.

Bacteremia

As with pneumonia, studies of pneumococcal bacteremia in adults and children have not shown an increase in mortality attributable to infection with penicillin-resistant vs. penicillin-susceptible strains. In a recent review of 922 pediatric cases of pneumococcal bacteremia, 14 of 730 isolates with known ceftriaxone susceptibilities were resistant to ceftriaxone *(13)*. Although children with ceftriaxone-nonsusceptible isolates were more likely to be febrile at follow-up than those with ceftriaxone-susceptible organisms (67% vs. 24%, $p = 0.04$), there was no significant difference for other endpoints. Penicillin, cefuroxime, cefotaxime, and ceftriaxone achieve levels well above 2.0 μg/mL for several hours after standard doses. Thus in the normal host these drugs should be effective for the majority of cases of pneumococcal bacteremia caused by resistant strains. Many experts recommend the same therapy for both pneumonia and bacteremia caused by antibiotic-resistant *S. pneumoniae.*

Otitis Media and Sinusitis

The upper respiratory tract is the most common site of pneumococcal infections. Although the majority of studies dealing with antibiotic-resistant pneumococci have been in otitis media, their therapeutic findings probably also apply to sinusitis. An 80–85% efficacy rate can be expected in treating otitis media using commonly prescribed antibiotics when the concentrations of the drug in the middle ear exceed the MIC for the infecting strain for 40–50% of the dosing interval *(14)*. Trimethoprim–sulfamethoxazole penetrates the middle ear poorly, and many penicillin-resistant pneumococci are also resistant to this combination. Pneumococcal cross-resistance to both penicillin and macrolides is also common, limiting the potential utility of erythromycin, clarithromycin, or azithromycin for treatment of otitis media or sinusitis.

Many experts still consider amoxicillin the drug of choice for treating otitis media. An increased dose (60–80 mg/kg/d) has been recommended for routine first-line therapy in children with moderately severe acute otitis media but are not toxic *(8)*. Alternative agents should be considered if high-dose amoxicillin therapy fails. Cefuroxime, cefprozil, and amoxicillin–clavulanate have been successful for the treatment of otitis media caused by pneumococci nonsusceptible to penicillin. Clindamycin is quite active against most of these strains and may be effective in this setting. Intramuscular ceftriaxone for at least 3 consecutive days is another option *(8)*.

STAPHYLOCOCCUS

Staphylococcus is a member of the family Micrococcaceae. These Gram-positive cocci, 0.7–1.2 mm in diameter, take their name from their tendency to grow in grape-like clusters in solid media although they may appear singly, in pairs, or in chains of fewer than five organisms. *Staphylococcus* is characterized by a positive test for catalase, and *S. aureus* is characterized by the presence of coagulase enzymes. Coagulase-negative species are quite numerous and include the frequently isolated *S. epidermidis* and *S. saprophyticus.*

Staphylococci produce many enzymes and toxins that may contribute to their pathogenicity. Catalase may counteract the host defense mechanism of oxygen radical production important in phagocytic killing. Coagulase promotes formation of fibrin networks that contributes to abscess formation. The β-lactamases are discussed in the following paragraphs. Toxins may exert their effect through enzymatic action or by induction of cytokines. α-Toxin is one of several membrane damaging toxins (α, β, γ, δ). It acts upon many cells including erythrocytes, leukocytes, and platelets and can cause osmotic cell death by producing pores in cell membranes. Leucocidin is a two-component toxin that affects the phagocytic and lysosomal membranes of leukocytes.

The epidermolytic toxin exfolatin is responsible for the epidermolysis of staphylococcal scalded skin syndrome (SSSS). Composed of either a chromosomal or a plasmid-derived toxin, exfolatin produces an intraepidermal blister at the granular cell layer. The five heat-stable enterotoxins (A–E) are responsible for staphylococcal food poisoning. They act by increasing peristalsis, which results in diarrhea. They may also produce central nervous system sympathetic activation to cause vomiting. Enterotoxin F is identical to toxic shock syndrome toxin-1 (TSST-1), an exotoxin responsible for the staphylococcal toxic shock syndrome (TSS). The enterotoxins, including TSST-1, and the epidermolytic toxins can affect, usually by activation, T lymphocytes. The resulting production of cytokines can produce fever, hypotension, shock, multiple organ failure, and death. These superantigen interactions result in increased production of interleukin-1, tumor necrosis factor-α, and interferon-γ.

The introduction of penicillin revolutionized the treatment of staphylococcal infections. Not long after the introduction of penicillin, strains with resistance to this agent were described. Sensitivity to penicillin in hospital strains is now rare and present in <20% of community isolates. Penicillin resistance is due to the production of β-lactamase, an enzyme with the ability to open the β-lactam ring and thereby inactivate antibiotics whose mechanism of action is dependent upon it. Multiple types of β-lactamases have been described. Most of these are inducible and carried on plasmids.

Semisynthetic agents resistant to β-lactamase, that is, methicillin, nafcillin, and the isoxazolyl penicillins oxacillin, cloxacillin, and dicloxacillin, are available and are effective for treatment of many infections due to *S. aureus.* Strains with resistance to the semisynthetic penicillinase-resistant penicillins, referred to as methicillin-resistant *Staphylococcus aureus* (MRSA), were first reported in Europe in 1961 *(15).* This intrinsic resistance results from the production of an altered PBP referred to as penicillin binding protein 2a (PBP 2a, PBP 2′). It is carried on the *mecA* gene and is transmitted chromosomally. MRSA is defined as an isolate with an oxacillin MIC of >4 μg/mL. The initial strains of MRSA were often resistant to multiple classes of antibi-

otics. During the 1970s, multiply resistant MRSA declined for reasons that are not clear. Subsequently, MRSA strains again emerged in several countries of Europe, Australia, and in the United States *(16)*. The virulence of MRSA strains varies somewhat but usually is not greater than that of methicillin-susceptible (MSSA) strains. After adjustment for major confounders, MRSA bacteremia appears to impact in-hospital mortality to the same extent as MSSA bacteremia *(17)*.

Concern that staphylococci would acquire resistance to vancomycin followed the identification of vancomycin resistance in other Gram-positive bacteria (*see* the section on *Enterococcus*). This raised the prospect of a return to the preantibiotic era when staphylococcal infections were a frequent cause of death. The *vanA* gene, which confers vancomycin resistance in enterococci, has been transferred to *S. aureus* via plasmids experimentally *(18)* and *S. aureus* strains with resistance to vancomycin can be produced in the laboratory *(19)*. The breakpoints for vancomycin established by the National Committee for Clinical Laboratory Standards are as follows: susceptible, < 4 μg/mL; intermediate, 8–16 μg/mL; and resistant, ≥ 32 μg/mL. In Japan in 1996, a strain of MRSA was recovered from a child after prolonged therapy with various combinations of vancomycin, aminoglycoside, and ampicillin–sulbactam for a surgical wound infection *(20)*. This strain exhibited a vancomycin MIC of 8 μg/mL. In the United States in 1997, the first MRSA isolate with an intermediate level of susceptibility to vancomycin (VISA) was recovered from an ambulatory peritoneal dialysis patient after prolonged treatment with vancomycin for peritonitis. A second VISA clinical isolate in the United States was reported later in 1997 associated with bloodstream infection following long-term MRSA colonization and repeated MRSA infections treated with vancomycin *(21)*. Neither of these isolates contained the *vanA* gene. The mechanism of resistance in these VISA strains is not yet known but suspected to involve an alternation in the cell wall *(22)*. Electron microscopy of clinical VISA isolates grown in the presence of vancomycin has revealed the presence of large quantities of surface material with staining properties similar to those of cell wall *(23)*. These thickened cell walls may have the capacity to absorb vancomycin but prevent it from reaching the site of active cell wall synthesis. In vitro studies of combinations of vancomycin with various β-lactam antibiotics at clinically achievable levels revealed good activity against a single clinically derived VISA strain.

The VISA isolates from Japan and the United States remained susceptible to various other available agents. To date, no clinical isolate of *S. aureus* with full resistance to vancomycin (MIC > 32 μg/mL) has been reported. It is desirable to identify strains of *S. aureus* with reduced susceptibility to vancomycin. Depending on the susceptibility pattern, site of infection, and response to conventional therapy, patients may be recommended for experimental therapies. Appropriate infection control measures to prevent the spread of *S. aureus* with reduced susceptibility to vancomycin should be instituted and epidemiologic and laboratory investigations should be undertaken *(24)*.

Colonization with staphylococci may begin shortly after birth in the neonate affecting the umbilical stump, perineum, skin in general, and gastrointestinal tract. Children and up to 40% of adults may become carriers. Most often the anterior nares is the reservoir but the rectum, perineum, and pharynx are also sites of carriage. The carrier state may be intermittent and is more prevalent in those with recurrent exposure to the organism. Those individuals who carry the organism are predisposed to subsequent

staphylococcal infection. Vaginal carriage of *S. aureus* occurs in nearly 10% of adult premenopausal women *(25).*

Staphylococcal infection results in acute inflammation with recruitment of polymorphonuclear leukocytes. Vascular compromise and tissue necrosis lead to abscess formation. Localized staphylococcal infections of the skin without rash are associated with poor hygiene, minor trauma, maceration, and underlying skin disorders. They tend to occur around the hair follicle. The conditions include folliculitis, furuncles, carbuncles, impetigo, hydradenitis suppurativa, mastitis, and wound infections. Advancing pyodermas include cellulitis, lymphangitis, lymphadenitis, and fasciitis. Local care of these conditions is mandatory with gentle cleansing and appropriate dressings to prevent spread of infectious material. Fluctuant areas should be surgically drained. Systemic antibiotic therapy is warranted when fever or systemic symptoms develop; lesions are large, numerous, or spreading; the face is involved; or if the patient has underlying medical problems such as valvular heart disease.

The localized staphylococcal skin infections with rash include SSSS and TSS. SSSS typically occurs in children < 5 yr of age presenting with bullous impetigo. TSS occurring in menstruating women has declined dramatically since the removal of hyperabsorbent tampons from the market in the early 1980s. Nonmenstrual TSS may occur as a result of vaginal colonization with toxin-secreting staphylococci but also follows surgery or other trauma to the skin, may be nosocomial, and appears more likely to result in renal or central nervous system complications *(26).* Treatment of TSS requires aggressive fluid replacement to support blood pressure and restore organ perfusion. Removal of the vaginal tampon, if present, and obtaining material for culture are recommended.

Staphylococci may be involved in respiratory tract infections. Despite their frequent nasal colonization, they are infrequently involved in sinusitis or otitis and do not cause pharyngitis. Staphylococcal pneumonia can occur from direct spread from the upper airways or via a hematogenous route. It may follow viral respiratory illness, especially influenza. As a nosocomial infection of debilitated patients, staphylococcal pneumonia carries a high mortality rate. Staphylococci are frequent causes of septic bursitis, septic arthritis, and osteomyelitis. These infections may occur from hematogenous spread or direct contiguous invasion of long bones, vertebral bodies, or disc spaces. Parenteral antibiotics are mandatory for serious staphylococcal infections.

Whenever a penicillin-susceptible strain of *S. aureus* requires treatment, penicillin is the drug of choice. Strains producing β-lactamase should be treated with a semisynthetic penicillin such as nafcillin or oxacillin. Patients with a history of delayed type hypersensitivity to penicillins may be treated with a cephalosporin such as cefazolin or cephalothin. Any MRSA infection that requires antibiotic therapy should be treated with vancomycin. Patients intolerant of vancomycin may be treated with fluoroquinolones, trimethoprim–sulfamethoxazole, clindamycin, or minocycline. These agents are not as effective as vancomycin, and resistance to fluoroquinolones may develop during therapy. Rifampin is useful as an antistaphylococcal drug but because resistance develops quickly, it should not be used alone. Bloodstream infections with *S. aureus* may result from an extravascular source that gains access to the vascular compartment. Bacteremia may also result from direct infection of the vascular space through a vascular access device or introduction in the course of substance abuse. In

nearly one-third of cases of staphylococcal bacteremia, no source of the infection is identified. Treatment of the source of the bacteremia or removal of intravascular devices should be pursued promptly.

The recommended length of therapy for staphylococcal bacteremia is controversial. Early studies suggested treatment courses of 4–6 wk to prevent relapse and endocarditis. Subsequently, courses as short as 2 wk have been recommended if the source of the bacteremia can be readily removed, for example, an intravenous catheter, and there is no evidence of endocarditis *(27,28).* More recently Lowy reviewed concerns about the validity of data used to justify short-course therapy and the underdiagnosis of endocarditis in this setting *(29).*

The development of endocarditis complicates therapy and increases mortality. The addition of an aminoglycoside for synergistic killing of bacteria has been shown to clear bacteremia more quickly than regimens without the combination. However, no change in mortality has been documented *(30).* Failure to control infection, myocardial abscess formation, and heart failure are indications for surgery in patients with endocarditis.

ENTEROCOCCUS

Members of the genus *Enterococcus* were formerly classified with the Lancefield group D streptococci. Growth at extremes of temperature, salinity, and alkalinity as well as hydrolysis of esculin in the presence of bile characterize these organisms. More recently genetic techniques have been used to clarify the taxonomy. These facultatively anaerobic Gram-positive cocci are usually found in the gastrointestinal and biliary tracts, vagina, and male urethra. Historically not considered pathogenic in humans, enterococci now represent significant causes of nosocomial and urinary tract infections. Of the more than 12 species identified, *E. faecalis* and *E. faecium* are the most important in human infection.

Because of their ability to survive harsh conditions, enterococci can persist in the environment *(31,32).* Adherence to host structures (cardiac valves, renal epithelial cells) facilitates the development of endocarditis and urinary tract infection. Antibiotic resistance plays a role in the ability of enterococci to cause superinfection in the presence of broad-spectrum antimicrobials.

Enterococci exhibit variable resistance to many antimicrobial agents commonly utilized to treat Gram-positive infections. All enterococci exhibit relative resistance to β-lactam antibiotics. Against *E. faecalis,* the MIC of ampicillin, penicillin, and piperacillin may be 1, 2, and 2 μg/mL, respectively. The cephalosporins are even less active. This resistance is present even in strains not exposed to antimicrobials and results from the reduced affinity of penicillin binding protein 5 (PBP-5) for these agents. In addition, exposure to these cell wall active agents can result in the rapid acquisition of tolerance in enterococci.

In the 1980s, enterococci resistant to glycopeptide antibiotics (vancomycin-resistant enterococci, VRE) were initially described in Europe and soon thereafter in the United States. Glycopeptide antibiotics inhibit cell wall synthesis by two mechanisms. First, they are such large molecules that they can physically block the transfer of peptidoglycan precursors to the growing chain, but this effect is not substantial. The glycopeptides also block the crosslinking of peptidoglycan chains which normally occurs through a pentapeptide with a D-Ala–D-Ala terminus. Acquired resistance requires that

the organism acquire a gene cluster that encodes for a series of coordinated biochemical events, rather than a single mutation. Different gene clusters produce specific resistance phenotypes. The VANA class, characterized by high-level resistance to vancomycin and teicoplanin, is the most common phenotype. It is inducible by either vancomycin or teicoplanin. The *vanA* gene produces crosslinking peptides with altered terminal sequences (D-Ala–D-lactate) that have reduced affinity for glycopeptides and thereby result in resistance to these agents. The VANB class is characterized by variable vancomycin resistance with preserved teicoplanin susceptibility. These chromosomal genes are inducible by vancomycin. Both of these classes of resistance are transferable and have been detected mainly in *E. faecalis* and *E. faecium.* Vancomycin resistance may be an intrinsic characteristic and not transferable. A VANC phenotype is found on chromosomes of species less frequently isolated from clinical specimens. It is constitutive and conveys relatively low levels of vancomycin resistance without resistance to teicoplanin.

The prevalence of VRE in the United States is increasing both in and out of the intensive care setting. Several studies have examined risk factors for VRE colonization or infection utilizing multivariate analyses. Significant indicators include exposure to vancomycin or ciprofloxacin, severity of illness as reflected by higher APACHE II scores, percentage of hospital days exposed to antibiotics *(33)*, hematologic malignancy, and bone marrow transplantation *(34,35).* Numerous other studies emphasize the importance of underlying illnesses (including liver or bone marrow transplantation, renal failure, diabetes); severity of illness reflected by prolonged hospitalization with invasive procedures; and exposure to multiple antibiotics including broad-spectrum β-lactams, agents with anaerobic activity, and especially intravenous vancomycin (reviewed in ref. *36*).

In a retrospective cohort study, VRE bacteremia was found to have an attributable mortality of 37% compared with 31% in vancomycin-susceptible enterococcal bacteremia *(37).* Corresponding values for coagulase-negative staphylococcal bacteremia and candidemia were 14% and 38%, respectively. Although there are conflicting data regarding mortality due to bacteremia with VRE compared with vancomycin-susceptible strains, the former may persist longer in the bloodstream and at the primary site and be more likely to recur compared with the latter *(34,38,39).*

The urinary tract is the site most frequently infected by enterococci. Clinical conditions include cystitis, pyelonephritis, perinephric abscess, and prostatitis. Most of these infections are nosocomial and associated with urinary tract instrumentation. They infrequently result in bacteremia. Enterococcal bacteremia may result from cholangitis, intravascular catheters, intraabdominal infection, and wounds including diabetic and decubitus ulcers and thermal injuries. Nosocomial bacteremia is more often polymicrobial and less likely to produce endocarditis than that acquired in the community. Most cases of endocarditis occur in patients with underlying valve abnormalities or prosthetic valves; however, normal valves may become infected as well. Other than endocarditis, enterococci rarely produce metastatic infection.

Although commonly found in polymicrobial abdominal and pelvic infections, the exact contribution of enterococci to these processes is not well understood. Similarly, differentiating enterococcal colonization from infection when present in polymicrobial surgical wounds or in diabetic or decubitus ulcers may be difficult. Enterococci have

been reported to cause spontaneous peritonitis in patients with nephrosis and cirrhosis as well as in patients undergoing ambulatory peritoneal dialysis. Enterococcal meningitis is rare, occurring in patients with altered central nervous system anatomy from trauma or surgery. The respiratory tract is also rarely affected by enterococci, generally in severely debilitated patients.

The synergistic combination of a cell wall active agent, such as ampicillin, with an aminoglycoside has been the standard treatment for enterococcal infections in which bactericidal activity is required (endocarditis, meningitis). Gentamicin has been utilized, as resistance to other aminoglycosides has been described. Although clinical benefit for the synergistic combinations has been documented for endocarditis, many other serious enterococcal infections are also treated with combination therapy *(36).* In patients allergic to penicillin, vancomycin plus an aminoglycoside is appropriate for treatment of infection due to susceptible strains.

Vancomycin resistance presents major challenges to the clinician. *E. faecalis* usually retains susceptibility to ampicillin or penicillin despite resistance to vancomycin and aminoglycosides. The loss of a synergistic combination makes treatment of endocarditis or meningitis in this setting problematic *(40).* Endocarditis due to vancomycin-resistant *E. faecalis* has been successfully treated with high-dose ampicillin (24 g/d) by continuous infusion *(41).* Vancomycin-resistant *E. faecium* may be even more difficult to treat, as these strains are often resistant to ampicillin, penicillin, aminoglycosides, and other available antimicrobial agents. Some strains may retain susceptibility to selected agents, for example, doxycycline *(42),* chloramphenicol *(43),* rifampin *(44),* or quinolones *(45).* These agents have been used alone and in combination to treat more serious enterococcal infections *(46).* These various regimens are bacteriostatic, however, and would be expected to be suboptimal for endocarditis or meningitis. Most enterococci remain susceptible to nitrofurantoin even if resistant to vancomycin. This agent may be useful for treatment of urinary tract infections due to VRE.

Quinupristin–dalfopristin (Synercid®) consists of a combination of drugs that belong to the streptogramin class of antibiotics *(47).* Individually these drugs are considered bacteriostatic but in combination have synergistic bactericidal activity against many Gram-positive organisms *(48).* The proposed mechanism of action is prevention of protein synthesis by binding to the 50S ribosomal subunit and inhibition of peptidyl tRNA synthetase. Quinupristin–dalfopristin is bacteriostatic for enterococci in general. It has very limited activity against *E. faecalis* preventing its clinical use to treat infections caused by recovered enterococcal species. It has converted patient cultures to negative for vancomycin-resistant *E. faecium* in several instances, but mortality rates appear to remain high *(49).*

Linezolid (Zyvox®) is a new agent of the oxazolidinone class of antibiotics. It also inhibits protein synthesis by binding at the 50S ribosome *(50)* but prevents formation of the protein synthesis initiation complex *(51).* Although bacteriostatic for enterococci, its level of activity as assessed by MIC studies does not appear to be affected by the presence of resistance to other antibiotics *(52).* Linezolid may prove useful in the treatment of clinical infections due to VRE and other resistant Gram-positive organisms.

Given the limited therapeutic options available currently and in the foreseeable future, and the increasing incidence of resistant enterococcal infections, it seems reasonable to attempt to limit the spread of these organisms by pursuing infection control

policies and practices within individual institutions that have a reasonable chance of success. Such recommendations have been published and shown to be effective although difficult to implement *(53,54).*

Key Points

- Pneumococcus may be penicillin susceptible (MIC ≤ .06 μg/mL), intermediate (0.1–1.0 μg/mL), or highly resistant (≥ 2.0 μg/mL).
- Because of possible pneumococcal resistance, empiric therapy for meningitis should include a third-generation cephalosporin (cefotaxine or ceftriaxone) + vancomycin ± rifampin.
- MRSA (oxacillin MIC > 4 μg/mL) infections should be treated with vancomycin; emergence of VISA is a concern.
- Some VRE infections may respond to high-dose ampicillin + an aminoglycoside or Synercid®, but infectious disease consultation is advisable.

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3
Gram-Negative Bacteria

Robert P. Rapp and Kenneth E. Record

INTRODUCTION

The cell wall of Gram-negative bacteria has a very distinctive layered look under the electron microscope and is dramatically different from the Gram-positive cell wall. The inner layer consists of a thin peptidoglycan layer; the outer layer or outer membrane is a protein containing bilayer. The inner component of the outer membrane consists of lipids and the outer layer is composed of macromolecules known as lipopolysaccharide (LPS) or endotoxin. The LPS layer serves as a lipid barrier to water-soluble molecules, preventing their passage into the periplasmic space. Water-filled channels known as "porin channels" are located at regular intervals in the outer membrane. These porin channels allow certain ions and molecules, including antimicrobial agents, to pass through the outer membrane. One of the major mechanisms of resistance in Gram-negative bacteria is the inability of an antibiotic to pass through either the LPS layer or via the porin channels. If antimicrobial agents cannot gain entrance into the Gram-negative cell then the target sites for these agents cannot be accessed and resistance is seen. Based on the chemical structure of the molecule, some antimicrobial agents can pass via the porin channels and some cannot. For example, the chemical structure and ionic charge on penicillin G allows the drug to pass through the porin channels of *Neisseria* species but it cannot pass through the porin channels of most other Gram-negative bacteria, thus limiting its Gram-negative spectrum. Adding an amino group to the penicillin molecule creates ampicillin, which dramatically expands the spectrum of activity to include many Gram-negative bacteria by virtue of better porin channel penetration.

Other factors that contribute to pathogenicity include production of a wide array of exotoxins and enzymes that cause many different specific and nonspecific signs and symptoms harmful to the host. For example, enterohemorrhagic *Escherichia coli* (0157:H57) produces several potent exotoxins known as shigalike toxins that are absorbed into the bloodstream and cause organ-specific damage including the hemolytic – uremic syndrome. In contrast, the urinary pathogen *Proteus mirabilis* produces no exotoxins but produces an enzyme known as urease. Urease splits urea to form ammonium hydroxide which creates an alkaline urine, thus neutralizing the acid-

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Table 1
Examples of Intrinsic (Natural) Resistance to Selected Antimicrobial Agents

Bacteria	Antimicrobial Agent	Mechanism
Escherichia coli	Penicillin	Cannot penetrate the porin channels to gain entrance into the bacterial cell
Gram-negative bacteria	Vancomycin	Cannot penetrate the porin channels to gain entrance into the bacterial cell
Pseudomonas aeruginosa	Imipenem and meropenem	Specific porin channels missing that are required for drug penetration

ity that inhibits the growth of many other bacteria. In addition, the alkaline urine can facilitate urolithiasis when magnesium ammonium phosphate salts precipitate out because these salts are less soluble in the more alkaline urine. Gram-negative bacteria virulence can also be mediated via adhesion factors, capsule formation, and the presence of flagella that provide antigenic variation and mobility.

RESISTANCE

Antimicrobial resistance in bacteria can be present even before a drug has been used—so-called intrinsic resistance *(1,2)* (Table 1). Alternatively, if bacteria are exposed to an antimicrobial agent, resistance can then develop and is termed acquired resistance *(3,4)* (Table 2). "Multidrug resistance" is also an important concept *(5–8).* Genetic expression of resistance to one drug can lead to expression of genetic resistance to multiple drugs. For Gram-negative bacteria, the best example of multidrug resistance has occurred in some isolates of *Pseudomonas aeruginosa* with resistance to virtually all antipseudomonal drugs *(9,11).* As a result, in some cases of multidrug resistant *P. aeruginosa,* drugs such as colistin and polymyxin B may be the only effective therapy. Unfortunately, at present there are no new classes of antimicrobial agents in United States Food and Drug Administration (FDA) class III trials for multidrug resistant *P. aeruginosa.*

For Gram-negative bacteria, there are several types of resistance that are important clinically. These include:

1. Production of β-lactamase enzymes that hydrolyze the β-lactam ring of penicillins, cephalosporins, monobactams, and carbapenems
2. Alterations of the enzymes involved in nucleic acid metabolism (DNA gyrase and topoisomerase) which may result in resistance to fluoroquinolones
3. Cell wall permeability resistance which occurs because of the inability of antibiotics to pass (either actively or passively) through porin channels
4. Modifications of the 50S and 30S ribosomal subunit
5. Efflux systems in which the antibiotic enters the bacterial cell but is pumped out by an active pumping system
6. Production of other enzymes that chemically alter the antibiotic, for example, as seen with aminoglycosides, macrolides, or chloramphenicol

Table 2
Examples of Acquired Resistance to Selected Antimicrobial Agents

Bacteria	Antimicrobial Agent	Mechanism
Klebsiella pneumonia	Ceftazidime	Common TEM and SHV enzymes mutate to ESBLs that hydrolyze ceftazidime and other β-lactams.
Pseudomonas aeruginosa	Imipenem, meropenem	Loss of outer membrane proteins that serve as porin channels that makes the bacteria impermeable to the carbapenem
Stenotrophomonas maltophilia	Imipenem–meropenem	Production of metallo-—lactamases that hydrolyze carbapenems

TEM, common plasmid mediated β-lactamase produced by many Gram-negative bacteria; SHV, plasmid mediated β-lactamase produced by *Klebsiella pneumoniae* and other Gram-negative bacteria; ESBL, extended-spectrum β-lactamase.

TREATMENT OF INFECTIONS CAUSED BY GRAM-NEGATIVE BACTERIA

Table 3 lists the initial choice of antibiotics for serious invasive Gram-negative infections. These choices take into consideration common resistance patterns and are intended as an initial guide for clinicians until the results of susceptibility testing are known. The management of Gram-negative infections has changed as a result of the emergence of resistant organisms, as summarized in the following sections.

Gram-Negative Bacteria with β-Lactamase-Mediated Resistance

β-Lactamases are enzymes that are capable of altering the structure of the β-lactam antibiotics *(12).* Figure 1 illustrates the site of β-lactam hydrolysis of the lactam bond in penicillins and cephalosporins. The resulting chemical alteration renders the structure incapable of binding to and inhibiting the penicillin-binding proteins (PBPs). One of the first classifications of β-lactamases that proved clinically useful was developed by Richmond and Sykes in 1973 *(13)* (Table 4). This classification is based on the genetic origin of the enzyme (plasmid or chromosomal), how the enzyme is produced (constitutive or inducible), and the preferred substrate profile (penicillins or cephalosporins). An enzyme that is inducible is one in which the amount of enzyme produced increases when the bacteria is exposed to an inducer (a β-lactam antibiotic that induces the enzyme). An enzyme that is produced constitutively cannot be induced and is produced at about the same level all the time. The genetic origin of the enzyme is also important in that chromosomally mediated enzymes cannot be passed between genus of bacteria and stay in the daughter cells, whereas those that are plasmid mediated can be passed to different bacteria by transferring the plasmid during sexual conjugation. Other classifications of these enzymes have been proposed, including the classification by Bush *(14)* (Table 5). In addition, specific types of enzymes may also be named based on individuals or substrates. For example, the TEM enzymes are so named because a Dutch girl who had an infection with a bacteria that produced this

Table 3
Initial Choice of Antibiotics for Serious Invasive Gram-Negative Infections

Infecting Gram-Negative Bacteria	First-Line Drugs of Choice	Alternative Drugs	Modifying Factors/Comments
Acinetobacter spp.	Imipenem, meropenem	Piperacillin, ciprofloxacin, trimethoprim–sulfamethoxazole	In seriously ill patients, consider adding a second drug either an aminoglycoside or fluoroquinolone.
Bacteroides fragilis	Metronidazole, clindamycin, BLIC	Imipenem, meropenem, cefoxitin	Most strains are β-lactamase (+)
Bordatella henselae	Cipro Azithro	Trimethoprim–sulfamethoxazole, clarithromycin	For cat-scratch disease
Bartonella pertussis	Erythromycin	Trimethoprim–sulfamethoxazole	For whooping cough
Burkholderia cepacia	Trimethoprim–sulfamethoxazole	Ceftazidime, chloramphenicol	Formerly called *Pseudomonas cepacia*
Enterobacter spp.	Imipenem, meropenem	Third-generation cephalosporin, piperacillin–tazobactam ciprofloxacin	In seriously ill patients, consider adding a second drug usually an aminoglycoside or fluoroquinolone.
Escherichia coli	Third-generation cephalosporin, fluoroquinolone, or BLIC	Trimethoprim–sulfamethoxazole, aztreonam	For uncomplicated urinary tract infections trimethoprim–sulfamethoxazole
Hemophilus influenzae	Cefotaxime, ceftriaxone	Cefuroxime, BLIC, fluoroquinolone	For meningitis, use only cefotaxime or ceftriaxone.
Klebsiella pneumoniae	Third-generation cephalosporin	Imipenem, meropenem, piperacillin–tazobactam, aztreonam, ciprofloxacin	In seriously ill patients, consider adding a second drug, usually an aminoglycoside or fluoroquinolone.
Legionella spp.	Azithromycin, fluoroquinolone	Doxycycline, erythromycin	Rifampin added to regimen may give additional benefit.

Moraxella catarrhalis	Macrolide, trimethoprim–sulfamethoxazole, doxycycline	Fluoroquinolone, amoxicillin/clavulanic acid, ceftriaxone, cefuroxime axetil	β-Lactamase hydrolyzes ampicillin and first-generation cephalosporins.
Neisseria gonorrheae	Ceftriaxone, ciprofloxacin, ofloxacin, cefixime	Cefotaxime, spectinomycin	β-lactamase (+) strains vary widely in different geographic locations.
Neisseria meningitidis	Penicillin G	Ceftriaxone, cefotaxime	Rare strains can be relatively resistant to penicillin.
Proteus (indole$^+$) Including *Providentia rettgeri, Morganella morganii,* and *Proteus vulgaris*	Third-generation cephalosporin	Imipenem, meropenem, piperacillin /tazobactam, ciprofloxacin, aztreonam	In seriously ill patients, consider adding a second drug, usually an aminoglycoside or fluoroquinolone.
Proteus mirabilis	Ampicillin or amoxicillin (β-lactamase(–) strains)	First- or second-generation cephalosporin, BLIC, aztreonam, fluoroquinolone	For acute uncomplicated UTI, trimethoprim–sulfamethoxazole
Providencia stuartii	Third-generation cephalosporin	Imipenem, meropenem, piperacillin–tazobactam, aztreonam, ciprofloxacin	For seriously ill patients, consider adding a second drug either an aminoglycoside or fluoroquinolone.
Pseudomonas aeruginosa	Piperacillin + an aminoglycoside (gentamicin, tobramycin, or amikacin)	Cefepime, ciprofloxacin, imipenem, or meropenem, + aminoglycoside	For serious infections, two drugs are usually recommended. For UTI, if susceptible, ciprofloxacin
Serratia spp.	Imipenem, meropenem	Third-generation cephalosporin, piperacillin, aztreonam, ciprofloxacin	In seriously ill patients, consider adding a second drug, either an aminoglycoside or fluoroquinolone.
Stenotrophomonas maltophilia	Trimethoprim–sulfamethoxazole	Ticarcillin–clavulanic acid, ceftazidime, or minocycline, aztreonam + Ticar-clav	Very antimicrobial resistant bacteria; therapy must be guided by susceptibility tests.

BLIC, β-Lactamase inhibitor combination (ampicillin–sulbactam, ticarcillin–clavulanic acid, piperacillin–tazobactam).

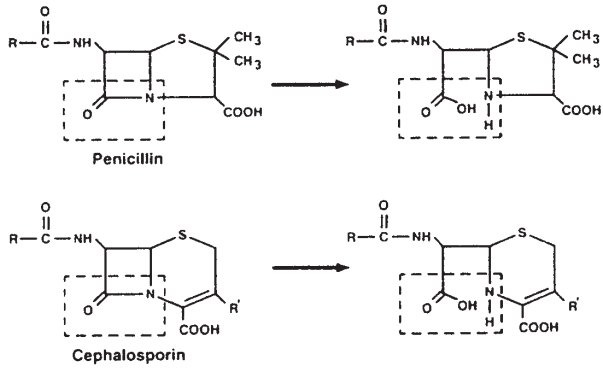

Fig. 1. Sites of β-lactamase hydrolysis of penicillins and cephalosporins.

Table 4
Modified Richmond and Sykes Classification of β-Lactamases

Richmond–Sykes Class	Examples of Bacteria that Produce the Enzyme	Genetic Location	Genetic Expression
I	*Pseudomonas aeruginosa* *Serratia marcescens* *Enterobacter* spp. *Proteus vulgaris* *Providentia* spp. *Citrobacter* spp. *Acinetobacter* spp.	Chromosomal	Inducible
II	*Escherichia coli* Proteus mirabilis	Chromosomal	Constitutive
III	*Klebsiella pneumoniae* *Escherichia coli* *Hemophilus influenzae* *Neisseria gonorrhoeae* *Pseudomonas* spp.	Plasmid	Constitutive
IV	*Klebsiella* spp.	Chromosomal	Constitutive
V	*Escherichia coli* *Pseudomonas* spp.	Plasmid	Constitutive
VI	*Bacteroides fragilis*	Plasmid and chromosomal	Constitutive

enzyme was named Temomera *(15,16).* Currently more than 70 TEM enzymes have been described in the literature.

Richmond and Sykes class I enzymes are cephalosporinases that hydrolyze first- and second-generation cephalosporins but also hydrolyze penicillins. Most class I enzymes

Table 5
Classification of β-Lactamases from Jacoby and Archer

β-Lactamase Production	Examples of Bacteria Affected	β-Lactams Affected	β-Lactam Not Affected
Common plasmid-mediated β-lactamase	Many Gram-negative bacteria	Ampicillin, ticarcillin, piperacillin, first-generation cephalosporins	Cefotetan, cefoxitin, imipenem, meropenem, third-generation cephalosporins, aztreonam
Plasmid-mediated extended-spectrum β-lactamases related to the TEM or SHV family	*Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae*	Above listed agents, aztreonam, cefotaxime, ceftazidime, ceftriaxone, ceftizoxime, cefuroxime	Cefotetan, cefoxitin, imipenem, meropenem, β-lactamase inhibitors
Chromosomal β-lactamases produced constitutive	*Pseudomonas aeruginosa, Enterobacter cloacae, Serratia marcescens*	Above listed agents, cefoxitin, cefotetan	Imipenem, meropenem
Extended-spectrum β-lactamases related to AmpC	*Stenotrophomonas maltophilia, Bacteroides fragilis*	Imipenem, meropenem	Variable
Carbapenem-hydrolyzing chromosomal β-lactamase	*Serratia marcescens Enterobacter cloacae*	Imipenem, meropenem	Variable

are produced by nosocomial bacteria and are chromosomally mediated. The stability of third-generation cephalosporins against class I enzyme-producing bacteria occurs because of the effectiveness of the side chains in inhibiting these enzymes. These enzymes are inducible, and under the influence of third-generation cephalosporins that are strong β-lactamase inducers, hyperproduction of the enzyme occurs through a mutational event, resulting in the loss of the repressor gene that controls production of the enzyme *(17,18).* The bacteria, following loss of the repressor gene, then produce more and more of the enzyme until hydrolysis of the drug occurs, and resistance develops, usually during therapy. Thus, bacteria, such as *Enterobacter cloacae,* that are initially susceptible to a drug such as ceftazidime can become resistant during therapy. This type of resistance is known as "stable derepression" and when such isolates cause serious infection, they usually remain susceptible to carbapenem antibiotics such as imipenem–cilastatin or meropenem *(19).*

TEM enzymes are included in the Richmond and Sykes class II–IV β-lactamases and are usually plasmid mediated. These enzymes hydrolyze all penicillins (penicillin, ampicillin, ticarcillin, piperacillin) and some first-generation cephalosporins. Sulfhydryl variable (SHV) enzymes are also included in the Richmond and Sykes class II–IV category and are also encoded on the plasmid. SHV enzymes hydrolyze penicillin and ampicillin but the side chains of ticarcillin and piperacillin offer some stability. TEM and SHV enzymes are produced by a variety of bacteria (predominately community-acquired organisms).

Most recent has been the recognition of extended-spectrum β-lactamases (ESBLs) *(20).* ESBLs are mutations of common TEM and SHV enzymes that occur under the selection pressure of broad-spectrum cephalosporins such as ceftazidime, ceftriaxone, or cefotaxime. Most ESBLs are inhibited by the carbapenem core structures (imipenem or meropenem), and are also inhibited by the three β-lactamase inhibitors, sulbactam, clavulanic acid, and tazobactam *(21).* However, as a response to the increased use of penicillin–β-lactamase inhibitor combinations, additional mutations of common TEM enzymes have now been reported. These so-called inhibitor-resistant TEMS (IRTs) are not inhibited by any of the three available β-lactamase inhibitors. While such enzymes are rare at present, it is reasonable to expect that as the use of drugs such as ticarcillin–clavulanic acid, ampicillin–sulbactam, piperacillin–tazobactam, and amoxacillin–clavulanic acid increases, the incidence of IRTs will continue to increase. In a like manner, as the use of carbapenem antibiotics increases, the number of bacteria that produce so-called carbapenase enzymes will also increase. Table 6 gives examples of β-lactamase-induced resistance in Gram-negative bacteria.

There are three basic ways to inhibit a β-lactamase. First, alteration/addition of side chains to the basic β-lactam core prevents the enzyme from hydrolyzing the lactam bond *(22).* As a general rule, the rank order stability of drugs to common β-lactamases based on side chains is: penicillins < first-generation cephalosporins < second-generation cephalosporins < third-generation cephalosporins. A second way to inhibit a β-lactamase is to alter the β-lactam core. The penicillin β-lactam ring is the easiest to hydrolyze followed by the cephalosporin ring, followed by the monobactam ring, followed by the carbapenem ring. A third method of β-lactamase inhibition is the addition of a β-lactamase inhibitor to a β-lactamase unstable antibiotic such as a penicillin. There are at present four such antibiotics, ampicillin–sulbactam, amoxacillin–clavulanic acid, ticarcillin–clavulanic acid, and piperacillin–tazobactam. Although these β-lactamase inhibitors differ in their potency and clinical dose, they all inhibit Richmond and Sykes class II–VI enzymes but have no inhibitory effect on class I enzymes. Table 7 lists Gram-negative bacteria that produce β-lactamases that are usually inhibited by the β-lactamase inhibitors along with the percentage of isolates that produced β-lactamase at the University of Kentucky Hospital during 1998. Only the side chains on third-generation cephalosporins or chemical alteration of the β-lactam core to either a monobactam (aztreonam) or a carbapenem (imipenem or meropenem) can inhibit class I enzymes.

ESBLs result from the selection pressure of third-generation cephalosporins *(23). Klebsiella pneumoniae* is the most frequently implicated bacteria followed by *Escherichia coli.* ESBL production has been reported in many other Gram-negative bacteria as well. In one ICU study, *K. pneumoniae* resistance to ceftazidime increased

Table 6
Examples of β-Lactamase-Induced Resistance in Common Bacteria Based on the Resistance of Different β-Lactam Antibiotics to Hydrolysis.*

Example of Resistance	Possible Antimicrobial Choices	Comments
Escherichia coli resistant to ampicillin	First-, second-, or third generation cephalosporins. BLICs, imipenem or meropenem, aztreonam	Activity ranking third-generation> second-generation> first generation
Klebsiella pneumoniae or *Escherichia coli* or other extended-spectrum β-lactamase producing Gram-negative bacteria resistant to third-generation cephalosporins	Imipenem, meropenem	Confirmation test for ESBL should be confirmed by microbiology—imipenem or meropenem is drug of choice.
Enterobacter spp. resistant to third-generation cephalosporin	Imipenem or meropenem, cefepime—not all isolates are susceptible to cefepime	Most likely hyperproduction of class I β-lactamase (stable derepression)
Pseudomonas aeruginosa resistant to antipseudomonas third-generation cephalosporins	Imipenem, meropenem, ciprofloxacin—based on susceptibility testing. Polymyxin B or colistin as last resort	Most likely hyperproduction of class I β-lactamase (stable derepression)

*This table does not cover choices for non-β-lactam drugs which could also be used for β-lactamase producing isolates. Other classes of antimicrobial agents such as fluoroquinolones and aminoglycosides may be effective. For bacteremic or neutropenic patients, many infectious disease consultants would utilize two drugs active against the isolate, usually a β-lactam plus another drug from a non-β-lactam class of antimicrobial agents such as an aminoglycoside or a fluoroquinolone.

from 3.6% in 1990 to 14.4% in 1993 *(24).* Numerous outbreaks of ESBLs have been reported in the United States and around the world *(25,26).* Intervention strategies to decrease the incidence of ESBL-producing bacteria include a reduction in the use of third-generation cephalosporins and increased use of drugs that do not induce ESBL production *(27,28).* Such agents include the penicillin–β-lacatamase inhibitor combinations and/or the carbapenems.

Recently the National Committee on Clinical Laboratory Standards (NCCLS) has published methods to both screen for and confirm the presence of an ESBL-producing bacteria *(29).* For example, the clinical microbiology laboratory can use cefotaxime, ceftriaxone, ceftazidime, aztreonam, or cefpodoxime as a screen at 2 μg/mL to detect

Table 7
Bacteria that Produce β-Lactamases that Are Usually Inhibited by the β-Lactamase Inhibitors Clavulanic Acid, Sulbactam, and Tazobactam and the Percent of Isolates that Produce Them at University Hospital University of Kentucky[a] or from the Literature[b]

Bacteria	Percent of Isolates that Produce the β-Lactamase
Escherichia coli	42[a]
Klebsiella pneumoniae	100[a]
Proteus mirabilis	15[a]
Hemophilus influenzae	45[a]
Staphylococcus aureus	93[a]
Bacteroides fragilis	>90[b]
Moraxella catarrhalis	95[b]

Data from University of Kentucky Hospital Antibiogram—1998.

ESBLs. For confirmation, a disk containing ceftazidime can be placed on a lawn of the bacteria next to an amoxacillin–clavulanic disk. Susceptibility will be restored (zone-of-inhibition) on the side of the ceftazidime disk that is closest to the amoxacillin–clavulanic disk (Fig. 2). Alternatively, an E-test strip containing on one end ceftazidime alone, and on the other end ceftazidime plus clavulanic acid, will also confirm the presence of an ESBL. The E-test confirmation is also shown in Fig. 2. One mutation in the amino acid chain of a TEM-1 enzyme can produce an ESBL and lead to resistance to third-generation cephalosporins.

Gram-Negative Bacteria with Resistance Due to Altered DNA Gyrase and Topoisomerase

Fluoroquinolone antimicrobial agents exert their bactericidal effect by inhibition of the essential bacterial enzymes DNA gyrase or topoisomerase IV *(30).* DNA gyrase controls DNA supercoiling, and topoisomerase IV controls decantenation of interlinked daughter chromosomes following DNA replication. Both of these enzymes are tetramers composed of two subunits. Two genes have been identified in mutations of the DNA gyrase subunits, *gyrA* and *gyrB.* Most often mutations in *gyrA* and, in a few instances, in *gyrB* result in fluoroquinolone resistance. Two genes have been identified in topoisomerase IV and include the *parC* and *parE* genes. Inhibition of either of these enzymes is a lethal event to the bacteria. Quinolone antimicrobial agents may also have additional mechanisms to inhibit bacterial DNA synthesis, including the ability to cause breaks in the double-strand DNA linkage.

Generally, mutations in *gyrA* are more important for acquisition of a quinolone-resistant phenotype in Gram-negative bacteria, while mutations in *parC* are more important for Gram-positive bacteria *(31–33).* Mutations in any of these target genes might be sufficient for the development of quinolone resistance but isolates that are highly resistant appear to have acquired multiple mutations more commonly than originally anticipated. Quinolones can also be rendered ineffective by efflux resistance in which the drug is pumped out of the bacterial cell by a multidrug efflux system (pump) *(34).* Bacteria with these multidrug-resistant genes are uniquitously distributed and can be selected by both

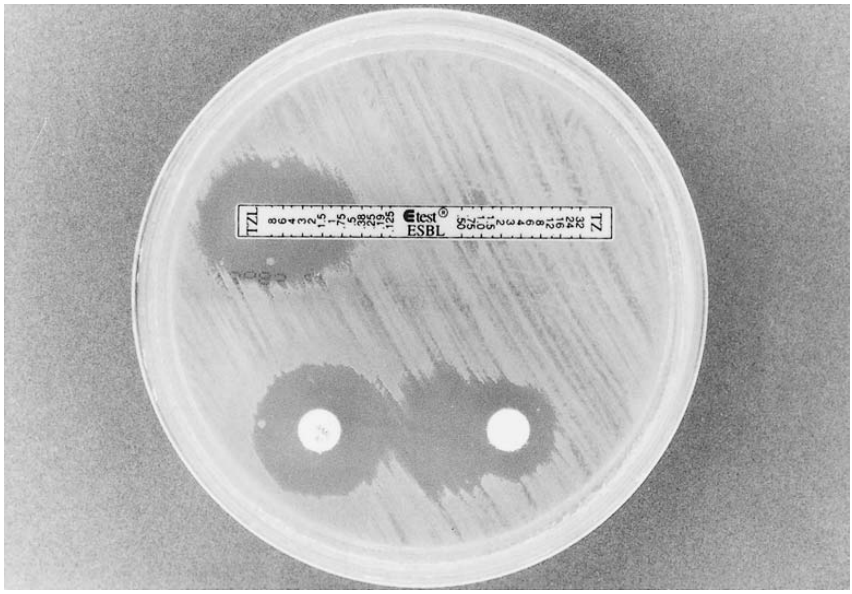

Fig. 2. Examples of two methods to confirm a clavulanic acid inhibitable ESBL phenotype strain. The lower disk is an approximation method (25 mm between 30 μg of ceftazidime and amoxicillin–clavulanic 20/10 disks); note the enhanced zone. The upper E-test with ceftazidime strip with and without a fixed concentration of 2 μg/mL of clavulanic acid; note ellipse around the strip with the inhibitor. (Courtesy of Dr. Ron Jones, University of Iowa College of Medicine.)

antimicrobial and nonantimicrobial compounds. Thus, resistance to fluoroquinolones can occur even without drug exposure and antibiotic selection pressure.

For Gram-negative bacteria, the most common mechanism of quinolone resistance is mutation of a target enzyme so that it no longer binds the fluoroquinolone. Fluoroquinolone resistance also occurs owing to decreased penetration through the Gram-negative cell wall. Efflux mechanisms can also lead to resistance (usually low level) to fluoroquinolones in Gram-negative bacteria. One or more of these mechanisms have led to resistant isolates of *E. coli, Salmonella* spp., *Klebsiella* spp., *P. aeruginosa, Neisseria gonorrhoeae, Campylobacter* spp., *Helicobacter pylori, Serratia marcescens, Morganella morganii, Proteus mirabilis, Burkholderia cepacia,* and *Stenotrophomonas maltiphilia.*

Quinolones and fluoroquinolones are excellent antimicrobial agents that have been effective in treatment of a wide variety of Gram-negative infections. Their popularity is enhanced by their effectiveness when given by the oral route and by the popularity of so-called "I.V. antimicrobial switch programs," which switch hospitalized patients to oral therapy as soon as the oral dosing form can be tolerated. This can be done because the high oral bioavailiabity of fluoroquinones generally gives the same peak blood levels as the intravenous dosing form. Unfortunately, cross-resistance is very common. In

other words, Gram-negative isolates resistant to ciprofloxacin are usually cross-resistant to all other fluoroquinolones. Although many new fluoquinolones have been introduced in the past several years, the activity of ciprofloxacin against most Gram-negative bacteria is still equal to or better than virtually all of the new agents. In the United States, ciprofloxacin remains the most active fluoroquinolone against *P. aeruginosa,* with about 70–80% of isolates being susceptible. In other countries, particularly in Europe, recent reports indicate susceptibility rates as low as 17.1%, whereas susceptibilities to levofloxacin are higher but still less than 50%. With these high rates of resistance, the use of fluoquinolones as one component of combination therapy for serious *P. aeruginosa* infections must be approached with caution and guided by local susceptibily rates. Because cross-resistance is common, when resistance occurs, it is usually necessary to use alternative antibiotics. Many fluoroquinolone-resistant isolates are also resistant to other classes of antimicrobial agents. Table 8 lists the fluoroquinolones active against Gram-negative bacteria.

Toxicity problems associated with the newer fluoroquinolone agents continue to evolve. Serious adverse effects include phototoxicity associated with sparfloxacin and liver toxicity associated with trovafloxacin. It is vitally important for all clinicians to report unexpected cases of drug toxicity to the United States Food and Drug Administration. Fluoroquinolones remain active against a wide variety of Gram-negative bacteria including those causing community-acquired respiratory tract infections such as *Hemophilus influenzae* and *Moraxella catarrhalis.* They are also active against many nosocomial bacteria as well, including isolates of *E. coli, S. marcesens,* and *Enterobacter* spp. For *P. aeruginosa,* resistance rates have increased, and empiric therapy must be guided by local susceptibility rates with the realization that many isolates are now resistant. Although newer fluoroquinolones have increased activity against many Gram-positive bacteria, older fluoquinolones such as ciprofloxacin remain the most active agents against most Gram-negative bacteria.

Aminoglycoside-Resistant Gram-Negative Bacteria

Aminoglycosides are rapidly bactericidal owing to their ability to inhibit protein synthesis and disrupt the integrity of the bacteria cell membrane *(35–37).* Aminoglycosides bind to the outer membrane and passively diffuse into Gram-negative bacilli through porin channels. Once in the cytoplasm, aminoglycosides move rapidly to bind bacterial ribosomes and cause an incorporation of incorrect amino acids into developing polypeptide chains.

As with other classes of antibiotics, resistance to aminoglycosides can be either intrinsic or acquired. An example of intrinsic resistance is the lack of antimicrobial activity of aminoglycosides against anaerobic bacteria. Acquired resistance to aminoglycosides can occur through a combination of three mechanisms: first, an alteration in membrane permeability; second, alteration in the target site; and third, enzymatic modification of the aminoglycoside *(38).* Enzymatic modification is the most common mechanism of resistance in Gram-negative organisms. Mutations in Gram-negative bacilli have been identified, altering membrane permeability and effectively reducing aminoglycoside uptake *(39).* Cross-resistance to all aminoglycosides occurs but the level of resistance is generally less (low level) than that seen with enzymatic modification. Another observation with altered membrane permeability is that susceptible bac-

Table 8
Fluoroquinolones Active Against Gram-Negative bacteria

Fluoroquinolone	Comment
Norfloxacin	Approved only for urinary tract infections, uncomplicated urethral and cervical gonorrheae, and prostatis caused by *Escherichia coli.* Available only for p.o. administration.
Ciprofloxacin	Many FDA approved indications for systemic, urinary tract, and sexually transmitted diseases. Oral bioavailability is approx 70%. Available for i.v. and p.o. administration.
Ofloxacin	Many FDA approved indications for systemic, urinary tract, and sexually transmitted diseases. Oral bioavailability > 90%. Available for i.v. and p.o. administration.
Lomefloxacin	Approved for acute exacerbations of chronic bronchitis but not if caused by *S. pneumoniae.* Also approved for urinary tract infections. Phototoxicity reactions have limited use. Available only for p.o. administration.
Enoxacin	Approved for urinary tract infections and uncomplicated gonorrheae. Available only for p.o. administration.

teria become refractory to the effects of aminoglycosides after the concentration-dependent killing phase. This is a temporary phenomenon and is referred to as adaptive resistance. Furthermore, altered permeability of the LPS component of the outer membrane (non-energy-dependent phase of uptake) may result in the development of resistance *(40).* Altered ribosomal binding from a single mutation of one protein (S12) of the 30S ribosomal subunit results in high-level resistance to streptomycin. However, this phenomenon is rare in clinical isolates of Gram-negative bacilli *(41).* Other aminoglycosides bind to several different proteins and are less likely to be affected by single mutational events. The genes responsible for the elaboration of modifying enzymes are associated with plasmids and transposable elements. Thus the resistance-producing genes can be spread rapidly, affecting not only aminoglycosides but other antibiotics as well.

Despite the development of a broader range of antibiotics for the treatment of Gram-negative bacterial infections, the aminoglycosides continue to play a vital role in therapy. Their rapid bactericidal action and additive/synergistic effects when combined with other agents still provide useful coverage in empirical therapy of severe infections, especially where *P. aeruginosa* is considered. The duration for which aminoglycosides may be used is limited by cumulative renal and ototoxicity.

Aminoglycosides combined with β-lactams are still a mainstay of therapy against some resistant Gram-negative bacteria causing life-threatening systemic infections, such as *P. aeruginosa* and *Enterobacter* spp. In many cases, such combinations offer synergistic activity against these bacteria. Because of the toxicity involved, the pharmacokinetic dosing of aminoglycosides is recommended with serum level and laboratory monitoring. For patients on longer therapy (> 10 d), baseline audiograms should be done and repeated on a weekly basis. Recent data support the single-daily dosing of

aminoglycosides rather than the traditional every 8–12-h regimens. Many reviews of this have recently been published *(42,43).* Therapy must be guided by in vitro susceptibility testing.

Gram-Negative Bacteria with Resistance Due to Alterations of Ribosomal Subunits

Macrolides have long been considered alternatives to β-lactam antimicrobial agents for patients who are allergic to β-lactams, but such use has been primarily for Gram-positive infections. In Gram-negative bacteria the outer cell envelope containing LPS acts as a major barrier to penetration by macrolide drugs, thus rendering many Gram-negative bacteria resistant to this class of drugs. An exception to this is azithromycin, which is able to penetrate the LPS layer of certain Gram-negative bacterial such as *Hemophilus influenzae (44).* Macrolide antimicrobial agents are active against a number of Gram-negative cocci and cocco–bacilli including *Neisseria gonorrhoeae, Neisseria meningitidis, Hemophilus ducreyi, Bordetella pertussis, Legionella pneumophila,* and *M. catarrhalis.*

The clinical usefulness of macrolides is well documented against *M. catarrhalis* causing respiratory tract infections. While macrolides are active against *N. gonorrheae,* they will not cure acute infections in a single dose. Because a major focus of infection with *N. meningitidis* is meningitis, and macrolides do not readily penetrate the cerebrospinal fluid, they are not useful in treatment of this infection. Erythromycin is not active enough against *H. influenzae* to be used for treatment. While clarithromycin is only moderately active against *H. influenzae,* the active metabolite, 14-hydroxyclarithromycin, is two to four times as active as the parent drug. Clarithromycin also provides useful activity against *Helicobacter pylori* but only in combination with other drugs. For *L. pneumophila,* macrolides are generally considered to be the drug of choice, but newer fluoroquinolones are also very active against this intracellular pathogen. Macrolide altering enzymes have also been described that are responsible for resistance in *E. coli.*

Facultative Gram-negative bacteria such as *Enterobacter* spp. and *P. aeruginosa* are resistant to clindamycin because the drug cannot penetrate the outer membrane layer of LPS. Modest intrinsic resistance also exists in species of *Hemophilus* and *Neisseria.* Other types of resistance mechanisms have also been described for clindamycin including the acquisition of RNA-methylating enzymes which alters the antibiotic binding site. Clindamycin has no specific indication for use against Gram-negative bacteria.

Chloramphenicol inhibits protein synthesis by binding to the 50S ribosomal subunit of RNA and is active against a wide variety of Gram-negative bacteria including *N. meningitidis, H. influenzae, Salmonella typhi, Stenotrophomonas maltophilia,* and *Burkholderia cepacia.* Unfortunately, concern about hemotological toxicities, including aplastic anemia, has limited the clinical use of the drug for the past several decades. When resistance occurs, it is usually due to inactivation by the plasmid-mediated enzyme chloramphenicol acetyltransferase.

Tetracycline

Tetracyclines exhibit a wide range of activity against many Gram-negative bacteria including *H. influenzae, N. gonorrhoeae,* and *E. coli.* However, widespread resistance

and the availability of effective alternative antimicrobial agents have limited their clinical usefulness. Several different types of tetracycline resistance have been described in Gram-negative bacteria including reduced uptake, energy-dependent efflux mechanisms, and ribosomal modification leading to decreased binding of the antibiotic. Some derivatives of tetracycline such as doxycycline and minocycline have been used for the treatment of serious cases of acne and even as secondary agents for community-acquired pneumonia because of their effectiveness against atypical bacteria.

Key Points

- Resistance to Gram-negative bacteria is increasing and may be due to a variety of mechanisms.
- Choice of antibiotics for Gram-negative infections should be guided by in vitro susceptibility testing and awareness of local resistance patterns
- Gram-negative bacteria that produce ESBLs should usually be treated with a carbapenem antibiotic.
- Quinolone resistance is increasing among Gram-negative bacteria, especially *Pseudomonas,* and practitioners should be aware of quinolone resistance rates in their community.
- Empiric therapy for *P. aeruginosa* infections may include antipseudomonal penicillins, antipseudomonal third-generation cephalosporins, aminoglycosides, antipseudomonal quinolones, or carbapenem drugs. For all serious infections caused by *P. aeruginosa,* a two-drug combination is recommended, with the most data available for the combination of an antipseudomonal β-lactam combined with an aminoglycoside.
- The use of antimicrobial combinations of the same class should generally be avoided because synergy is unlikely and the likelihood of antagonism is increased.

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4
Viruses

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INTRODUCTION

Several viral illnesses are commonly seen in outpatient settings and have substantial morbidity and for certain pathogens, mortality, associated with them. These include influenza, herpes viruses, varicella/zoster virus, and respiratory syncytial virus. Although epidemiologic evidence indicates that these viruses differentially affect the general population, they share a common characteristic of affecting a great number of people. The purpose of this chapter is to discuss these common viruses in the context of appropriate treatment.

INFLUENZA VIRUS

Influenza, caused by highly infectious RNA viruses of the orthomyxovirus family, is a major cause of morbidity and mortality among patients with chronic diseases and those over the age of 65 yr. Influenza A viruses are classified into subtypes based on two surface antigens; hemagglutinin (H) and neuraminidase (N). Changes in the H or N antigen account for the epidemiologic success of these viruses. Antigenic shift is the emergence of influenza A viruses with novel H or N antigens that occurs when human and/or animal strains undergo genetic reassortment and the new strain is then transmitted to humans. The worldwide outbreaks (pandemics) of 1918, 1957, 1968, and 1977 were caused by antigenic shifts. Antiagent drift is the sequential change in H and N antigens due to the selective pressure of increasing immunity in the population. Immunity to the surface antigens, especially hemagglutin, reduces the risk of infection or, if infection occurs, lessens the severity of the disease. Infection with one subtype, however, provides little protection against infection with other subtypes, and infection or vaccination with one strain does not result in immunity to distantly related strains of the same subtype because of antigenic drift. To a lesser extent this antigenic variation occurs in the more stable Influenza B viruses. Antigenic characteristics of circulating strains provide the basis for selecting the virus strains used in each year's influenza vaccine. Major epidemics of respiratory disease are caused by influenza virus strains not represented in that year's vaccine *(1–3).*

Epidemiology

Each year approximately 10–20% of the population in the United States develops influenza. Previous pandemics had the greatest morbidity and mortality among the sus-

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ceptible, often younger, population. In recent influenza seasons, especially when influenza A type H3N2 predominated, 80–90% of influenza-related deaths occurred in individuals >65 yr of age. Overall, influenza epidemics between 1972 and 1992 claimed the lives, on average, of 21,000 individuals each season. It is the fifth leading cause of death in individuals over 65 yr and the most common infectious cause of death in this country. Rates of disease are increased in individuals 65 yr of age or older and in those with underlying health problems. These high-risk groups are more likely to require hospitalization as the result of secondary complications such as bacterial pneumonia, worsening of chronic respiratory or cardiac disease, and primary viral pneumonia *(1,2,4).*

Disease Processes

During the initial evaluation of an influenzalike illness several entities must be considered in the differential diagnosis: respiratory syncytial virus, parainfluenza, adenovirus, enterovirus, mycoplasma, chlamydia, and streptococcal disease. Influenza is extremely contagious and is transmitted from person to person via small particle aerosols of virus-laden respiratory secretions expelled into the air by infected persons during coughing, sneezing, and talking. The abrupt onset of fever, myalgia, sore throat, and a nonproductive cough characterize the typical influenza infection. Symptoms usually last 1–5 d. Unlike other common respiratory illnesses, infection with influenza viruses causes severe malaise lasting several days. The symptoms vary based on age; children commonly present with cough, rhinorrhea, and croup, whereas adults present with cough, myalgia, sore throat, and headache. The elderly most commonly complain of cough alone or in combination with headache *(1–3).* Diagnosis of influenza is based on clinical signs and symptoms when an outbreak is occurring in the community at the time of presentation.

Treatment and Prevention

Treatment of influenza infections is targeted toward symptoms, with spontaneous recovery within 5–7 d. The typical therapy includes bed rest, oral hydration, acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) to reduce fever, headache, and myalgias, over-the-counter throat lozenges, intranasal anticholinergics, and systemic antihistamines and anticholinergics. Preventative measures along with antiviral drugs are used to shorten the disease course and decrease secondary complications *(5).*

Two approaches can be used in the United States to reduce the morbidity and mortality of influenza infection—immunoprophylaxis with inactivated, that is, formalin-killed, vaccine and chemoprophylaxis or therapy with an influenza antiviral.

Vaccine

Each year's vaccine contains three virus strains representing the viruses that are predicted to circulate in the United States during the upcoming influenza season. The vaccine usually contains two type A strains and one type B strain made from highly purified, inactivated egg-grown viruses. Following vaccination, the patient develops high titers of hemagglutinin-inhibition antibody which is protective against influenza strains in the vaccine or the closely related variants that may emerge during the influenza season. The maximum antibody response occurs in 2–4 wk and declines within 10 mo. The elderly and individuals with underlying chronic medical conditions may have a diminished antibody response to vaccination, and therefore can remain susceptible to influenza-related upper respiratory tract infections. Nevertheless, vaccina-

Table 1
Effectiveness of Influenza Vaccination

Population	Percent Illness Prevented	Percent Hospitalizations and Pneumonia Prevented	Percent Death Prevented
Healthy < 65	70–90%		
65 yr and older not in a chronic care facility		30–70%	
65 yr and older in a chronic care facility	30–40%	50–60%	80%

Data from ref. *(1)*.

tion can prevent lower respiratory involvement or other secondary complications. Vaccination in closed settings (i.e., nursing homes and chronic care facilities) results in "herd immunity" and, if done prior to the influenza season, can decrease the number of hospitalizations and secondary complications in this population (Table 1) *(1)*.

It is recommended that the following individuals have the influenza vaccine: (1) persons aged 65 yr and older; (2) residents of nursing homes or chronic care facilities who are at least 6 mo of age; (3) individuals 6 mo or older who have underlying medical conditions; (4) Individuals 6 mo to 18 yr of age who receive long-term aspirin therapy and have an increased risk for developing Reye's syndrome after being infected with influenza virus; (5) women who will be at or beyond 14 wk' gestation during the influenza season or at any stage if underlying medical conditions may result in secondary complications; and (6) employees of hospitals, outpatient settings, nursing homes, and other chronic care facilities that care for high-risk patients. To further decrease the risk of transmission, the household members of patients and employees should be vaccinated *(6)*.

HIV-positive individuals with high CD4 counts may benefit from vaccination. Approximately 80% of travelers who return to the United States with a febrile illness have commonly acquired diseases such as influenza; thus travelers may also benefit from vaccination.

Many patients are misinformed about the side effects of the influenza vaccine, and are therefore hesitant to receive the vaccine. The vaccine cannot cause influenza. Respiratory disease following vaccination represents coincidental infection unrelated to the vaccine. Known side effects include:

1. Soreness at the injection site: This is the most common side effect and usually lasts for only 2 d. It is generally mild and only rarely interferes with the individuals daily activity.
2. Systemic symptoms: Fever, malaise, and myalgia are more common in individuals who have never been exposed to the antigens in the vaccine (i.e., children). The reaction usually begins 6–12 h after the vaccination and lasts for 1–2 d.
3. Immediate reaction: This includes hives, angioedema, allergic asthma, and systemic anaphylaxis. These reactions are probably due to hypersensitivity to a component of the vaccine (i.e., residual egg products). Therefore, individuals with allergies to egg products should not be vaccinated.
4. Guillain-Barré syndrome: This entity has been difficult to prove as a true side effect of the influenza vaccine. The possible one or two cases per million vaccinations does not add significant risk to withholding the vaccine in individuals who are at high risk of

Table 2
Influenza Vaccine Dosing Recommendations

Age Group	Vaccine	Dose	Number of Doses[a]	Route
6–35 mo	Split virus only	0.25 cc	1 or 2	Intramuscular
3–8 yr	Split virus only	0.50 cc	1 or 2	Intramuscular
9–12 yr	Split virus only	0.50 cc	1	Intramuscular
> 12 yr	Split or whole virus	0.50 cc	1	Intramuscular

[a] For children under 9 yr of age who are receiving the vaccine for the first time, two doses should be administered 1 mo apart.

developing secondary complications. This is true even in those with a history of the disorder *(7,8).*

Because of the decline of immunity during the year and antigen variation seen year to year within the influenza virus, individuals should receive the vaccine every year. The optimal time for vaccination is October to mid-November. The activity of influenza in the United States usually peaks between late December and early March; therefore, vaccination in high-risk groups should not be administered earlier because antibody levels may decline within a few months of vaccination.

Influenza vaccine dosing recommendations are given in Table 2.

Antiviral Agents for Influenza

Amantadine hydrochloride and rimantadine hydrochloride are two antiviral agents available with specific activity against influenza A viruses. They interfere with the replication cycle of influenza A, but not influenza B, and when administered prophylactically to children and healthy adults before and throughout the epidemic period are 70–90% effective in preventing illness. They do not prevent subclinical infection; therefore, some individuals may develop protective immune responses.

Chemoprophylaxis is recommended for individuals who are at greatest risk for severe illness and complications if infected with influenza A and include:

1. High-risk persons who present after an outbreak of influenza A: These individuals should still be vaccinated, but the development of protective antibodies can take up to 2 wk. If these individuals have significant risk of secondary complications, chemoprophylaxis should be considered for a 2-wk interval. Antiviral therapy does not interfere with antibody response to the vaccine. If the patient is a child receiving the vaccine for the first time consider 6 wk of chemoprophylaxis (i.e., continue for 2 wk after the second vaccine injection).
2. Unvaccinated individuals who have contact with a high-risk group: These individuals should be vaccinated and given 2 wk of chemoprophylaxis. In an event that an outbreak occurs that may be due to a variant strain missed by the original vaccine, individuals working with this high-risk group should receive therapy throughout the peak period.
3. Immune deficiency: Individuals who are expected to have an inadequate antibody response and are at high risk for secondary complications should be given chemoprophylaxis throughout the peak influenza period.
4. Persons with contraindications for vaccination: High-risk individuals with severe anaphylactic hypersensitivity to egg protein or other vaccine component should be considered for chemoprophylaxis.

Table 3
Amantadine and Rimantadine Dosing Recommendations

Population	Type of Therapy	Amantadine	Rimantadine	Evidence
Child ≤ 45 kg or age 1–9 yr	Treatment	5 mg/kg/d up to 150 mg in two divided doses	Not approved for treatment	A
	Prophylaxis	5 mg/kg/day up to 150 mg in two divided doses	5 mg/kg/d up to 150 mg in two divided doses	A
Age 10–13 yr	Treatment	100 mg b.i.d.	Not approved for treatment	A
	Prophylaxis	100 mg b.i.d.	100 mg b.i.d.	A
Age 14–64 yr	Treatment	100 mg b.i.d.	100 mg b.i.d.	A
	Prophylaxis	100 mg b.i.d.	100 mg b.i.d.	A
Age ≥ 65 yr	Treatment	≤ 100 mg/d	100 or 200 mg/d	A
	Prophylaxis	≤ 100 mg/d	100 or 200 mg/d	A

Renal impairment	Creatinine Clearance mL/min/1.73 m^2	Dose	Creatinine Clearance mL/min/1.73 m^2	Dose
	30–50	200 mg on d 1, then 100 mg/q.d.	> 10	No change
	15–29	200 mg on d 1, then 100 mg/q.o.d.	≤ 10	100 mg/d
	< 15	200 mg every 7 d		
Liver dysfunction	No change		100 mg/d in severe cases	
Seizure	Close observation		Close observation	

Data from refs. *1,2.*

Multiple studies have shown that treatment with amantadine or rimantadine is effective in reducing the severity and duration of symptoms if given within 48 of illness (*see* Table 3 for dosing recommendations). Drug-resistant virus can emerge after treatment of children or adults and then transmitted to family contacts. Consideration should be given to withholding treatment in an acutely ill person, especially a child, when prophylaxis may need to be given to a high-risk individual in the same household.

Side Effects and Toxicity

The associated effects seen with each of these medications are usually mild, cease after discontinuation, or diminish or disappear after the first week of therapy despite continuation.

Side effects when dosed at 200 mg/d to young healthy adults:

1. Amantadine:
   a. Gastrointestinal: nausea and anorexia
   b. CNS: nervousness, anxiety, difficulty concentrating, and lightheadedness
2. Rimantadine:
   a. Gastrointestinal: nausea and anorexia
   b. CNS: nervousness, anxiety, difficulty concentrating, and lightheadedness.

More severe side effects have been associated with high plasma concentrations of drug e.g. in patients with renal insufficiency, elderly patients on 200 mg/d dosing, and patients with seizure disorders and certain psychiatric disorders. These more serious side effects include seizures, agitation, hallucinations, delirium, and marked behavioral changes. Usually a decrease in dose results in fewer of these toxicities *(1).*

Future Options

Intranasal Vaccine

Although still in clinical trials, an intranasal, live-attenuated, cold-adapted, trivalent vaccine may represent an effective and convenient approach in children. Efficacy in individuals 1–5 yr of age ranged from 86% to 100% *(9,10).*

Zanamivir

Zanamivir is a sialic acid analog that selectively inhibits viral surface neuraminidase, an enzyme essential for viral replication, in both influenza A and B. The drug has demonstrated efficacy in patients with severe symptoms and a temperature > 38.2°C when therapy is initiated within 48 h of the signs and symptoms of infection. Treatment benefits include a decrease in clinically significant symptoms by 1–1.5 d. No effect was seen in patients who presented later in the disease process or presented without fever. Zanamivir was well tolerated except in patients with underlying chronic pulmonary disease, in whom the drug may cause bronchospasm and/or decline in lung function. Although no direct comparison studies have been done, in most patients zanamivir should have fewer side effects than amantadine or rimantadine.

Zanamivir is dosed 10 mg (two oral inhalations at 5 mg/inhalation) every 12 h for 5 d. The most common complaints during therapy included headache, nausea, vomiting, diarrhea, bronchitis, cough, sinusitis, dizziness, and ear and nasal symptoms. These adverse events occurred with similar frequencies in patients receiving zanamivir or placebo and are difficult to distinguish from the symptoms of influenza *(11–13).*

Tamiflu the prodrug Oseltamivir (GS4104), the first FDA-approved oral neuramidase inhibitor, has approval for the treatment of influenza types A and B. The indications for use of oseltamivir, dosed at 75 mg twice a day for 5 d, include acute uncomplicated illness in adults, who present within 48 h of becoming symptomatic. When given to individuals between the ages of 18 and 65 yr, a mean 1.3-d decrease in time to clinical improvement was observed compared to the placebo group. The major adverse events included nausea and vomiting with fewer than 1% of study patients discontinuing the medication. Typically, these events resolved after the first few doses without discontinuation of the medication and are minimized with coadministration of food.

Studies are still underway to assess efficacy when used as prophylaxis, the rate of resistance to the influenza virus, and the use in individuals with hepatic or renal dys-

function. In addition, data are limited concerning repetitive therapy, drug–drug interactions, overdose, individuals with influenza type B, and those with underlying medical conditions.

HERPES SIMPLEX VIRUSES

Herpes simplex viruses (HSV) are enveloped double-stranded DNA viruses in the herpesvirus family. HSV I and II have the capacity to invade and replicate in the central nervous system, establish latent infection, and recur in the presence of humoral and cell-mediated immunity. Latent stages of HSV I and II occur as a result of viral entry into sensory nerve endings following primary infection. The virus is then transported to the nuclei of sensory ganglia where, in the majority of patients, it remains for the life of the individual. Reactivation often follows local or systemic stimuli, that is, physical or emotional stress, fever, exposure to ultraviolet light, tissue damage, or immunosuppression. The spectrum of HSV disease includes primary and recurrent infections of mucous membranes (i.e., gingivostomatitis, herpes labialis, and genital HSV), keratoconjunctivitis, neonatal herpes, visceral HSV infections in immunocompromised hosts, and HSV encephalitis *(17,18).*

Epidemiology

More than one third of the world's population has recurrent HSV infection. The frequency of HSV I infections is influenced by geographic location, socioeconomic status, race, sex, and age. Individuals in developing countries and lower socioeconomic populations have evidence of seroconversion earlier in life, with approximately one third of children under the age of 5 yr having serologic evidence of HSV I infection. The prevalence of HSV I infection increases to 70–80% by early adolescence. Middle socioeconomic populations demonstrate a 20% seroconversion rate in children over 5 yr of age that increases to 40–60% by the second and third decades of life. University students have a 5–10% annual incidence of HSV I infections, compared to an approx 2% annual incidence of HSV II infections.

Herpes simplex virus type II is usually acquired through sexual contact. The annual incidence of HSV II infection is approx 500,000, with 40–60 million latently infected individuals in the United States. Gender, race, number of sexual partners, marital status, and place of residence affect the incidence of HSV II infections. Individuals who are divorced (compared to single or married) or live in cities (compared to suburbs) have a higher prevalence of HSV II. The seroprevalence is approx 10% from ages 15 to 29 yr and 35% by age 60 with a three- to fourfold higher rate in African-Americans as compared to Caucasians. The highest seroprevalence rates are among injection drug users (40–60%), female prostitutes (75%), and male homosexuals (83–95%). The number of lifetime sexual partners is directly correlated with acquisition of infection (Table 4).

Women have a higher rate of infection than men (Table 4). The estimated risk of transmission from a male with active lesions to a susceptible female after a single contact is 80%. Transmission between monogamous sexual partners with discordant infection status is 10–15% yearly. During pregnancy the rate of infection is approx 2% per gestation with transmission to the fetus related to shedding of the virus at the time of

Table 4
Serologic Evidence of HSV II Infection by Number of Partners

Number of Partners	Heterosexual Women	Heterosexual Men	Homosexual Men
1	<10%	0%	—
2–10	40%	20%	—
11–50	62%	35%	>60%
>50	>80%	70%	90%

delivery. Prevalence of viral shedding varies from 0.5% to 1% for all women at the time of delivery, irrespective of past history of HSV infection *(17)*.

Disease Processes

Mucocutaneous Infection

Transmission of HSV depends on intimate, personal contact between a susceptible individual and an individual who is excreting the virus. For infection to be initiated, the viruses must come into direct contact with mucosal surfaces or abraded skin. Following exposure to HSV I vesicular lesions on an erythematous base appear after an incubation period of 2–12 d (mean of 4 d). HSV may be shed from oral lesions for up to 23 d (mean of 7–10 d) and the symptoms may last for 2–3 wk. Asymptomatic infection is the rule rather than the exception in oral HSV infection. When symptomatic, primary infection presents with a fever of 101–104°F. In primary gingivostomatitis, only rarely in recurrent infection, submandibular lymphadenopathy can occur. Other common symptoms include sore throat and mouth, malaise, tender cervical lymphadenopathy, and the inability to eat. Children are more likely to present with painful buccal and gingival involvement and inability to tolerate liquids. The elderly often have a pharyngitis with mononucleosislike symptoms. On initial evaluation the physician must consider herpangina (usually due to coxsackieviruses), candida infections, Epstein–Barr virus mononucleosis, Stevens–Johnson syndrome, and lesions induced by chemotherapy or radiation therapy.

Recurrent infections are usually preceded by a prodrome of pain, burning, tingling, or itching approx 6 h prior to the eruption of vesicles. In recurrent oral–labial disease, the vesicles are typically found on the vermilion border of the lips. On presentation there are usually three to five vesicles that persist an average of 48 h before progressing to a pustular or ulcerative and crusting stage. Lesions last for 72–96 h with complete resolution in 8–10 days.

Primary HSV II genital infection typically presents as macules and papules that progress to vesicles, pustules, and ulcers. Virus is shed for 11–12 d and the lesions heal in approx 3 wk. Systemic complaints of fever, dysuria, localized inguinal lymphadenopathy, and malaise occur in about 70% of cases. Most infections go unrecognized but symptomatic infections are more severe in women. Symptoms of first-episode HSV II infections are decreased in the presence of antibodies to HSV I. Genital herpes caused by HSV I is less severe clinically and less likely to recur. In women, lesions appear on the vulva and are typically bilateral, but they can also involve the buttocks, perineum, vagina, and cervix. The primary infection can result in a urinary retention syndrome in 10–15% of the cases and an aseptic meningitis in 25%

of the cases. Men typically present with vesicular lesions superimposed on an erythematous base on the glans penis or the penile shaft. As in women, the thigh, buttocks, and perineum may be involved. Other complications occurring in both groups include sacral radiculomyelitis, neuralgias, and meningoencephalitis. Proctitis is more common in homosexual men following primary HSV II infection.

Recurrent infection is typically preceded by a prodrome often described as a local irritation. Three to five vesicles appear on the shaft of the penis in men, while women typically present with vulvar irritation. The duration of symptoms is typically 8–10 d with viral shedding lasting 2–5 d. Neurologic and systemic complications are uncommon in recurrent disease, but paresthesia and dysesthesias do occur. The frequency of these recurrences vary among individuals, but the more severe the primary infection the more likely and frequent are the recurrences. One third of patients will experience eight or nine episodes per year, one third will have four to seven, and one third will have two or three. Transmission of the virus can occur in both symptomatic and asymptomatic recurrences. Most HSV II infected individuals are unaware of the infection and the risk to their partners.

Other disorders seen with herpes viruses include eczema herpeticum among patients with underlying atopic dermatitis, herpes gladitorium, and herpetic whitlow. Both HSV I and II can trigger erythema multiforme *(17,18).*

Neonatal Disease

The incidence of neonatal HSV infection ranges from one case per 2000 to 5000 deliveries per year, resulting in 1500–2200 cases annually in the United States. The transmission from mother to fetus is influenced by four factors: (1) With initial or primary maternal infection the transmission rate is 30–50%, while with recurrent infection transmission is ≤ 3%. (2) Maternal antibody status prior to delivery influences the severity and the likelihood of transmission. (3) Rupture of membranes for more than 6 h can result in ascending infection of the neonate via the cervix. (4) Inoculation at the site of fetal scalp monitors.

The newborn typically acquires HSV from the mother, but relatives and hospital personnel with orolabial herpes can act as reservoirs of infection. Seventy-five to eighty percent of the infections are acquired through intrapartum contact with the infected genital secretions. The remainder of transmissions are due to postnatal acquisition and, rarely, *in utero* infections. Neonates infected *in utero* present with skin vesicles or scarring, ocular disease, and microencephaly or hydranencephaly. Because of the high mortality risk, these neonates should be diagnosed and treated within the first 24 h. Other neonatal HSV infections are include those localized to the skin, eye, and mouth, encephalitis with or without skin involvement and disseminated infection involving the central nervous system (CNS), lungs, liver, adrenal glands, skin, eye, and/or mouth *(17,19).*

HSV Keratoconjunctivitis

Herpes simplex virus is the most common cause of corneal opacification and infection-related visual loss in the industrialized world. HSV I is the major agent beyond the neonatal period. The incidence of new and recurrent episodes is 20.7 per 100,000 person-years. Primary infection is often asymptomatic and results in a latent infection in the trigeminal or other sensory ganglia. Recurrent viral shedding can be unilateral or bilateral and may be associated with preauricular adenopathy, photophobia, tearing,

eyelid edema, chemosis, or the pathognomonic branching dendritic lesions. Recurrent episodes are typically unilateral and occur at similar rates as herpes labialis. Infection may involve either superficial (eyelids, conjunctiva, or corneal surface) or deep (cornea or anterior uvea) structures. Infection of the deeper structures is more serious and may cause permanent visual loss. The length of active disease with the initial episode of keratitis averages 17.6 d, while recurrent episodes last on average, for 28.4 d. The visual outcome of epithelial disease is good. In 90% of involved eyes a visual acuity of 20/40 or better will be maintained *(17,20,21)*.

HIV and HSV

Genital herpes, typically HSV II, has been linked to both the acquisition and transmission of HIV-1 and is the most frequent sexually transmitted disease among HIV-1 seropositive individuals. Because the prevalence of HSV antibodies among injection drug users and men who have sex with men is high when HIV infection is detected, few cases of primary HSV infections occur in HIV-infected adults or adolescents. Reactivation of HSV in HIV-infected individuals is more frequent than in immunocompetent individuals and may result in multiple sites of shedding and chronic, persistent mucocutaneous disease. These lesions can present as large ulcerative lesions involving any area of the body but the genital and perirectal regions are the most common. Less frequently, HSV may result in CNS infection, bronchitis, pneumonitis, and disseminated disease. The severe forms of HSV infections (defined as mucocutaneous ulcers lasting > 1 mo or bronchitis, pneumonitis, or esophagitis among patients > 1 mo of age) are more likely to occur in those with CD4 counts of < 100 cells/mm^3 and were reported as AIDS-defining illnesses in 3.8% of children and 4.4% of adolescents and adults *(6–8)*.

CNS Infections

HSV accounts for 10–20% of all viral encephalitis cases and is the most common cause of fatal sporadic encephalitis in the United States. The incidence of this disease is three per 100,000 cases and, beyond the neonatal period, is typically caused by HSV I. HSV II can cause benign aseptic meningitis in adults, but patients present without the mental status changes or morbidity seen with HSV I. HSV encephalitis has an associated high morbidity and mortality even if diagnosed and treated early. Treated groups have a mortality of approx 30%, while untreated patients have a mortality that exceeds 70% with only 2.5% of survivors regaining normal neurologic function. Patients typically present with less than 1-wk duration of symptoms. Ninety percent of these patients present with fever and focal neurologic findings consisting of hemiparesis, dysphasia, aphasia, ataxia, or focal seizures. Patients may also have altered consciousness or unusual behavior. Although no pathognomonic signs exist, HSV encephalitis should be suspected in those with a progressively deteriorating level of consciousness in association with fever, an abnormal CSF profile, and focal neurological findings in the absence of other etiologies *(17,25)*.

HSV in Pregnancy

Approximately 1500–2200 cases of neonatal herpes occur each year in the United States, most often due to HSV II. Because of the high morbidity and mortality in untreated cases of neonatal infections, reduction in perinatal transmission is a major target in preventative care. Approximately 2% of susceptible women acquire HSV

Table 5
Rate of Maternal – Fetal Transmission

Maternal Infection	Fetal Infection Rate
Primary infection with active lesions at delivery	50%
Asymptomatic primary infection	33%
Recurrent infection with active lesions at delivery	3–4%
Asymptomatic recurrent infection	0.04%

infection during pregnancy, which can lead to an increased risk of preterm labor, intrauterine growth retardation, and spontaneous abortion. These infections occur throughout the course of pregnancy with 30% in the first, 30% in the second, and 40% in the third trimester. Those patients with the highest risk of acquiring the infection are young, single women with a history of previous sexually transmitted diseases. Brown et al. demonstrated no vertical transmission or increased pregnancy-related morbidity in women who were infected early in their pregnancy. Acquisition of the disease near the time of delivery, however, resulted in vertical transmission and complications. Table 5 reflects the rates of maternal–fetal transmission of HSV based on maternal infection *(18,19,26)*.

Treatment

No cure for HSV exists, but steps can be taken to prevent transmission and antiviral therapy is available to decrease viral shedding and healing time. The main issue concerning genital HSV transmission, however, is preventative care. Individuals with high-risk behavior and those with current infection, even if asymptomatic, should be educated on the proper use of condoms and behavioral changes to decrease the risk of spreading and acquiring this disease. In those with HSV infection, acyclovir, a synthetic acyclic purine nucleoside analog, is considered the standard of therapy. More recently, drugs with greater oral bioavailability, the prodrug valacyclovir (converted to acyclovir) and famciclovir (converted to penciclovir), have been licensed. Acyclovir has a safe toxicity profile and has been evaluated more completely, but it appears that the prodrugs have an equally safe profile. The major adverse effect from these medications is alteration of renal function caused by crystallization of the drug in renal tubules resulting in reversible elevation of serum creatinine and, less commonly, acute tubular necrosis. The risk of renal dysfunction is substantially increased in individuals who are dehydrated or have underlying renal insufficiency. When administered to rats or rabbits in equivalent therapeutic doses in humans, these drugs are not carcinogenic, mutagenic, teratogenic, or affect fertility. Further studies are required to completely assess the safety in pediatrics, pregnancy, and nursing mothers.

Therapy shortens the duration of viral shedding and length of time to healing when initiated within 24 h of onset. Even with early initiation of therapy, duration of symptoms and length of time to recurrence are not affected. Topical agents should be used only in mild cases while IV therapy is reserved for those with severe local disease or systemic complications. Table 6 describes the therapeutic options for HSV infections.

Table 6
Treatment of HSV Infections

Infection	Acyclovir	Valacyclovir	Famciclovir	Evidence
Genital HSV				
Initial episode	200 mg p.o. 5 × day × 5–10 d 5 mg/kg i.v. q8h × 5 d 5% ointment topically q6h × 7 d	1000 mg p.o. b.i.d × 5–10 d	250 mg p.o. t.i.d. × 5–10 d	A
Recurrent episode	200 mg p.o. 5× d × 5 d 400 mg p.o. t.i.d. × 5 d 800 mg p.o. b.i.d. × 5 d	500 mg p.o. b.i.d. × 5 d	125 mg p.o. b.i.d. × 5 d	A
Suppression	200 mg p.o. t.i.d. 400 mg p.o. b.i.d.	250 mg p.o. b.i.d. 500 mg p.o. q.d.	250 mg p.o. b.i.d.	A
Immunocompromised				
Initial episode	200–400 mg p.o. 5× d × 10 d 5 mg/kg i.v. q8h × 7–10 d	500 mg p.o. b.i.d. × 10–14 d	125–250 mg p.o. b.i.d. × 10–14 d	A
Recurrent episode	200–400 mg p.o. 5× d × 5–10 d	500 mg p.o. b.i.d. × 5–10 d	125–250 mg p.o. b.i.d. × 10–14 d	A
Suppression	200 mg p.o. t.i.d. 400 mg p.o. b.i.d.	500 mg p.o. q.d. 500 mg p.o. b.i.d.	125–250 mg p.o. b.i.d.	A
HSV encephalitis	10 mg/kg iv q8h × 10–14 d	—	—	A
Neonatal HSV	10 mg/kg i.v. q8h × 10–14 d	—	—	A
HSV in pregnancy	See the section on special cases			
HSV resistance	See the section on special cases			

Data from refs. *17,25,27,28.*

Suppressive therapy should be considered in individuals with more than six episodes per year or in those with severe cases. Therapy can be initiated in adherent patients at the start of prodrome symptoms to decrease the length of time to healing. Patients should continue safe sex behavior since asymptomatic shedding of the virus can continue despite suppressive therapy. The FDA has approved therapy for 12 mo with acyclovir, although studies have demonstrated efficacy with no cumulative toxicity over 5 y. Patients on suppressive therapy should have dose adjustments or trials of discontinuation of suppressive therapy every 12 mo to assess the need for continued therapy.

Special Cases

Pregnancy

Because the greatest risk of vertical transmission occurs near the time of delivery, patients should be educated on abstinence versus the use of condoms during the third trimester—especially if the status of the partner is unknown. The use of antiviral medication continues to be studied in this population. The FDA has categorized the current antiviral medications as class C (acyclovir) and class B (valacyclovir and famciclovir). Acyclovir crosses the placenta, concentrates in the amniotic fluid and breast milk, and achieves therapeutic levels in the fetus when given by the oral or intravenous route to the mother. Studies have demonstrated no increase in fetal complications even when acyclovir is given in the first trimester. Questions on the use of these agents should be directed to the appropriate pregnancy registry (famciclovir: 800–366–8900 ext. 5231 and acyclovir or valacyclovir: The registry is closed, but questions should be directed to 888–825–5249). Guidelines on the treatment of pregnant women remain controversial among experts in the field *(26,29–34).*

For treatment of a primary infection during the first and second trimesters, use standard doses for genital infections. Suppressive therapy over the last 4 wk of pregnancy may prevent recurrence at term, thereby decreasing the need for Cesarean section. Termination of pregnancy is not recommended for women who become pregnant while receiving antiviral therapy. If the primary infection occurs during the third trimester, Cesarean section should be considered in all patients, especially if symptoms occur within 4 wk of delivery. If Cesarean section is contraindicated or the membranes ruptured more than 4–6 h prior to a Cesarean section, antiviral therapy of mother and newborn may be indicated. In all patients considered at high risk for vertical transmission, minimize all procedures that could damage the newborns skin and create a portal of entry for infection (e.g., scalp electrodes, fetal blood sampling, and instrumental delivery).

For treatment of a recurrent infection, proceed with a normal vaginal delivery if genital lesions are not apparent at the time of delivery. Cultures during late gestation to predict viral shedding at term or cultures at the time of delivery are not indicated. If the patient presents at delivery with lesions, the risk of HSV transmission to the newborn must be assessed for each patient. The available evidence suggests that the risks of vaginal delivery for the fetus are small and must be set against the risks to the mother of a Cesarean section.

Resistance in Immunocompromised Patients (HIV, Bone Marrow Transplant Recipients, and Solid Organ Transplant Recipients)

The prevalence of acyclovir resistance in this population is approx 5%. Viral resistance is promoted by the degree of immunosuppression of the patient and by prolonged

use of acyclovir. If the virus is resistant to acyclovir, then it is likely resistant to valacyclovir and famciclovir as the mechanisms of resistance are similar *(35).* If the patient has not responded to initial therapy within 14 d, resistance should be suspected. The virus may be susceptible, but higher doses of medication or changing from acyclovir to one of the newer prodrugs with better bioavailability may be needed. Benefits from increasing acyclovir to 800 mg orally five times a day or dosing acyclovir as a continuous infusion at 1.5–2.0 mg/kg/h until the lesions have crusted have been demonstrated.

If these regimens fail, antiviral susceptibility testing may be indicated and alternative therapy with foscarnet or cidofovir considered. Foscarnet is considered first-line therapy in acyclovir-resistant infections. The major side effects are nephrotoxicity and mineral and electrolyte abnormalities, but these typically resolve with discontinuation. Foscarnet is dosed at 40 mg/kg intravenously every 8 h and should be dosed based on creatinine clearance. Therapy is continued until the lesions have crusted over and complete reepithelialization has occurred, usually after 2–3 wk of therapy. Cidofovir is currently approved for the treatment of cytomegalovirus disease and should be considered only in individuals who have failed high-dose acyclovir and foscarnet. The major adverse event is renal tubular toxicity. To diminish this nephrotoxicity, both hydration and probenecid dosed pre- and post-infusion are recommended. Cidofovir is dosed at 3–5 mg/kg intravenously every week for 2–4 wk. Once these lesions have resolved, recurrent infections are typically caused by acyclovir-sensitive virus; therefore, therapy with acyclovir or the prodrugs should be initiated as the first-line treatment *(28,36,37).*

VARICELLA-ZOSTER VIRUS

Like the herpes simplex viruses, varicella-zoster virus (VZV) is an enveloped, double-standed, DNA virus of the herpesvirus family. VZV causes two distinct clinical syndromes. Primary exposure to VZV results in varicella (chickenpox), a usually benign, highly contagious infection of children. Reactivation of latent VZV results in herpes zoster (shingles), an illness most commonly seen in adults over the age of 45 yr.

Epidemiology

VZV is spread from person to person by direct contact, as an aerosol from skin lesions, or in respiratory tract secretions. Virus enters through the mucosa of the upper respiratory tract or the conjunctiva. Transmission to susceptible hosts occurs from 2 d before appearance of the rash until the lesions crust. Of the 4 million cases of varicella per year, 33% occur in preschool children (1–4 yr of age) and 44% occur in school-age children (5–9 yr of age). The secondary attack rate is 90% among susceptible individuals in the same household. These secondary varicella cases within the family are usually more severe than the primary cases, likely because of the greater intensity of exposure. Only 5% of varicella infections are subclinical (i.e., without rash).

A history of varicella infection is a reliable marker for immunity, with a positive history 97–99% predictive of serologic immunity. Seventy-three to ninety-three percent of individuals with a negative history of varicella are also seropositive.

Nosocomial transmission of varicella is a serious and expensive healthcare problem. After exposure to varicella, susceptible employees can serve as vectors with transmission to patients. Varicella has been reported in hospital employees without direct contact with patients having active lesions but exposed to air from the patient's room *(38).*

Herpes zoster is more common in adults and the immunocompromised, 75% of cases occurring in those over the age of 45 yr. Immunocompetent children, adolescents, and young adults can develop herpes zoster, so a single episode in these individuals should not suggest underlying immunodeficiency. Herpes zoster may result in varicella in a susceptible host but exposure to someone with varicella does not cause herpes zoster.

Disease Processes

Varicella

Varicella in children is a self-limited disease of 4–5 d duration consisting of fever, malaise, and a generalized, pruritic, vesicular rash that starts on the face and scalp and then spreads to the trunk and later to the extremities. The average incubation period is 14–16 d but varies between 10 and 21 d. Successive crops of vesicular lesions appear over 2–4 d. If the vesicles do not rupture, they become purulent and then crust over. Complications from varicella include bacterial superinfection, especially β-hemolytic Group A streptococci, pneumonia, meningoencephalitis, cerebellar ataxia, and hepatitis. Reyes syndrome associated with aspirin use during VZV infection is now uncommon *(39).* Adolescent and adults are more likely to have severe disease and are at greater risk of varicella pneumonia and death.

Although perinatal infection is uncommon because most mothers are immune, intrauterine VZV infection may result in fetal varicella syndrome (low birth weight, cutaneous scarring, limb hypoplasia, microencephaly, cortical atrophy, chorioretinitis) if the infection occurs during the first half of the pregnancy. The incidence of fetal varicella syndrome with VZV infection in wk 1–12 is 0.4% and in wk 13–20, 2% *(40,41).* Varicella infection of the mother 5 d before to 2 d after delivery may result in severe varicella in 17–30% of newborns with a 31% risk of death if untreated. Passive immunization with varicella immune globulin (VZIG) is effective in reducing mortality.

Herpes Zoster

After primary infection, latent VZV persists within the sensory dorsal root ganglia. Herpes zoster presents as a unilateral vesicular rash distributed over one to three dermatomal segments. The rash usually crusts within 10 d and completely heals within a month. When the trigeminal nerve is involved, especially the ophthalmic branch, care must be taken because the eye may become involved and lead to dendritic keratitis, anterior uveitis, iridocyclitis, and panophthalmitis. The most common complication of herpes zoster is pain. Postherpetic neuralgia more often affects people over 50 yr of age and can be severe, lasting for weeks to months. In an immunocompromised host, reactivation of VZV may result in a disseminated infection with a generalized eruption and CNS, pulmonary, hepatic, and pancreatic involvement.

As the rash of varicella is so characteristic, the diagnosis is not difficult to make. The unilateral, dermatomal eruption of herpes zoster is also easy to recognize, although herpes simplex infection can mimic herpes zoster. Patients with herpes zoster may present with pain prior to the appearance of rash, making the diagnosis more difficult.

Treatment

Antiviral

Several drugs are now available for the treatment of VZV infections. Acyclovir, when given within 24 h of the appearance of the varicella rash, decreases the number of

days new lesions appear, duration of fever, and the severity of cutaneous and systemic signs and symptoms. Acyclovir does not, however, decrease transmission or reduce absence from school and is not recommended for the routine treatment of healthy children *(42)*. Because varicella is a more severe disease in adolescents, adults, and immunocompromised children, treatment with acyclovir is recommended *(43,44)*. Prophylaxis with acyclovir can prevent secondary cases among close contacts. In a placebo-controlled trial, 16% of ACV-treated patients developed varicella compared with 100% of controls *(45)*. Treatment must begin early because in the immunocompetent host, viral replication, which acyclovir inhibits, is no longer detectable 72 h after the rash appears.

Because therapeutic levels after oral administration are unreliable, intravenous acyclovir is recommended for severe VZV infections. Adequate hydration must be maintained during intravenous acyclovir administration to prevent ACV precipitation in the renal tubules resulting in acute renal failure.

Acyclovir is also useful in the treatment of herpes zoster. If given within 72 h of the appearance of rash, it will accelerate the rate of healing, reduce severity of disease, and diminish the incidence and severity of postherpetic neuralgia. Acyclovir is especially useful in treating people over the age of 50 who have a greater incidence of postherpetic neuralgia *(46)*. Although steroids do not protect against postherpetic neuralgia, adding steroids to acyclovir helps decrease the duration of acute pain and the return to daily living *(47)*.

Valacyclovir, a prodrug of acyclovir with better absorption and higher serum levels, can also be used *(48)*. Famciclovir, a prodrug of penciclovir, is effective in treating varicella and herpes zoster *(49)*. The advantages of valacyclovir and famciclovir is convenience. Both are dosed three times a day instead of five times per day as reqvired with acyclovir, leading to better patient adherence. Famciclovir and valacyclovir may decrease the duration of postherpetic neuralgia but not its incidence in elderly patients (*see* Table 7 for dosing recommendations).

Resistance to these three drugs is uncommon, but when resistance is present foscarnet, which acts by directly inhibiting the viral DNA polymerase, may be useful. The major toxicities of foscarnet are renal dysfunction and electrolyte imbalance.

Varicella Zoster Immune Globulin

VZIG provides the most benefit when administered as soon as possible, but if given within 96 h of exposure to someone with VZV disease, it may prevent or ameliorate varicella infection *(50)*. Protection lasts for 3 wk with a single dose of VZIG.

Vaccination

A live attenuated VZV vaccine has been developed and proven effective in preventing VZV infection. Unlike wild-type VZV, the vaccine strain causes a subclinical infection, leading to immunity that is 70–90% effective in preventing the symptoms of varicella. Transmission of the vaccine strain to others is rare but it is advisable for the vaccinee to avoid close contact with those at risk for severe complications of varicella. With the limited follow-up available, herpes zoster rates appear lower in vaccinees than those infected with wild-type VZV. The vaccine is also effective in preventing or modifying varicella infection if given within 3 d of exposure to VZV.

Table 7
Treatment of Varicella-Zoster Virus

Disease	Valacyclovir	Famciclovir	Acyclovir	Evidence
Varicella Immunocompetent host			20 mg/kg (maximum 800 mg) 4× daily for 5 d	A
Varicella Immunocompromised host			10 mg/kg i.v. every 8 h for 7–10 d	A
Herpes zoster Immunocompetent hosts	1 g 3 × daily for 7 d	500 mg 3× daily for 7 d	800 mg 5 × daily for 7 d	A
Herpes zoster Immunocompromised host			10 mg/kg i.v. every 8 h for 7 d	A
Herpes Zoster Immunocompromised host Resistant virus	Foscarnet 40 mg/kg i.v. 3 × times daily for 7–14 d			B

The Advisory Committee on Immunization (ACIP) has recommended that all children entering child care facilities and elementary schools have received VZV vaccine or have other evidence of varicella immunity (physician diagnosis of varicella, reliable history, or serologic evidence *(51)*. Because the risk of severe varicella is high in adolescents and adults, vaccine is indicated in susceptible individuals over the age of 12 at high risk for exposure including those living or working in environments where transmission of VZV is likely or can occur, those living in households with children, nonpregnant women of childbearing age, and international travelers.

Vaccine should not be given to patients with cellular immunodeficiencies because of the risk of severe vaccine associated varicella but VZV vaccine can be given to patients with humoral immunodeficiencies and asymptomatic or mildly symptomatic (age-specific $CD4^+$ T-lymphocyte percentage of ≥ 25%) HIV-infected children. Pregnant women should not receive the vaccine because of concerns of fetal varicella syndrome and the increased risk of severe varicella in late pregnancy. Routine universal VZV vaccination will decrease the booster effect from exposure to wild-type virus which may lead to waning immunity among vaccinees, thus requiring booster vaccinations to prevent severe varicella infections later in life.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is highly infectious and easily transmitted from person to person by close contact. The primary modes of transmission include direct

contact with large droplets of secretions (small particle aerosol is not a significant mode of transmission) and self-inoculation of eyes and nose by hands made infectious by touching contaminated objects. For example, RSV can be isolated from countertops more than 6 h after contact with an infected source such as nasal secretions. Other infectious media include rubber gloves (90 min), gowns (30 min), and hands (25 min). Good hand washing and proper disposal practices are, therefore, important as infected individuals shed the virus for 1–21 d (mean of 6.7 d) even if asymptomatic *(52,53)*.

Epidemiology

RSV infections are distributed worldwide and are the leading cause of lower respiratory tract infections (50–90% of bronchiolitis cases are due to RSV) in infants and young children. In the United States the season generally begins in November peaks from January to March and then continues through April to mid-May. Approximately 90,000 children are hospitalized and 4500 deaths occur annually in the United States due to the complications of RSV.

Fifty to sixty-nine percent of all children develop primary RSV infection by the age of 12 mo, with 15–22% having lower respiratory involvement. One-half to two percent will be hospitalized, with mortality ranging from 0.5% to 3.5%. By 2 yr of age 95% have been infected with RSV. Immunity following infection is short lived; therefore, reinfection occurs throughout life. Reinfection rates in preschool-aged children range from 40% to 70%, with approx 20% recurrences in school-aged children, adolescents, and adults.

Increased disease severity is associated with low socioeconomic status, ethnicity, male gender, young age, body mass of < 5 kg, prematurity, chronic lung disease, congenital heart disease especially in association with pulmonary hypertension, and T-cell immunodeficiency. Increased risks of acquiring the disease occur with a maternal education level of grade 12 or less, crowding (two or more individuals sharing a bedroom), school-age siblings, multiple births, lack of breastfeeding, passive smoke exposure, day-care attendance, and birth within 6 mo prior to an anticipated RSV season *(52,54)*.

Disease Process

The average incubation period of RSV is 5 d. Symptoms can range from coldlike symptoms to severe bronchiolitis or pneumonia with symptoms after reinfection typically being milder. The hallmark of infection involves the small intrapulmonary airways, with bronchiolitis being the most distinctive clinical syndrome. Lower respiratory tract infections are due to transfer of the virus from the upper respiratory tract and result in sloughing of the bronchiolar epithelium, hypersecretion of mucus, peribronchiolar mononuclear infiltration, and submucosal edema. The plugs of mucus and cellular debris lead to partial or complete airway obstruction, especially in the small lumens of infants. Following infection, the immunity to the RSV virus is transient and imperfect. Recurrent upper respiratory infections are probably due to the transitory nature of immunity of immunoglobulin A (IgA). In contrast, lower respiratory tract resistance appears to be more durable *(52)*.

Neonate

Newborns typically acquire RSV via contact with visitors and healthcare personnel. The clinical variation and rare clinical evidence of lower respiratory tract involvement

in individuals <3 wk of age is probably due to the presence of maternally derived neutralizing antibodies. Signs of upper respiratory tract infections occur in fewer than 50% of infected neonates and are highly variable and nonspecific. These clinical signs include poor feeding, lethargy, and irritability.

Young Infants

Infants younger than 1 yr of age who have low cord serum RSV antibody titers and are not breast fed have an increased risk of lower respiratory tract disease in the first 5 mo of life. One of the early manifestations in this age group following RSV infection is apnea, occurring more readily in infants who are <6 wk of age, are born prematurely, or have low arterial oxygenation saturations. Mechanical ventilation, if required, is necessary for approx 48 h with postextubation apnea being uncommon.

Infants with severe disease, but without an underlying medical condition, can be identified with six independent clinical and laboratory findings to predict those who would benefit from hospitalization: (1) Oxygen saturation of <95%, determined by pulse oximetry, is the best single objective predictor. (2) Atelectasis on chest radiograph. Typically, diffuse interstitial pneumonitis and hyperexpansion are apparent with this latter process being the hallmark of RSV infection. It occurs in 50% of hospitalized patients and may be the only radiographic finding in 15% of the cases. Twenty-five percent of children, especially younger infants, have subsegmental consolidation, typically in the right upper or middle lobe. (3) Respiratory rates ≥ 70 breaths per minute. (4) Gestational age <34 wk. (5) Age < 3 mo. (6) "Ill" or "toxic" appearance. If hospitalization is required, the length of stay is typically 4–7 d with full recovery at about 2 wk. Major complications include respiratory failure, apnea, and secondary bacterial infections. Long-term complications are minimal, with recurrent episodes of wheezing being the major clinical sequelae. Recurrences diminish after the first few years with no increased risk for airway hyperreactivity or pulmonary function abnormalities by the age of 8–12.

Young Children

Initial infections with RSV are typically symptomatic and range from a mild cold-like illness to severe bronchiolitis or pneumonia. These latter syndromes occur in 30–70% of cases following the initial exposure to RSV and can be difficult to differentiate, but the classic signs of bronchiolitis are wheezing and hyperexpansion of the lung. Typically, children have fever ranging from 38°C to 40°C during the first 2–4 d of the illness, nasal discharge, pharyngitis, and cough. Hoarseness and laryngitis are uncommon. By the time these children present to their local healthcare facility, lower respiratory tract symptoms are more prominent. These signs and symptoms are based on the severity of disease and can include increased cough, increased respiratory rate up to 80 breaths per minute with substernal and intercostal retractions during inspiration, a prolonged expiratory phase, hypoxemia typically without cyanosis, hyperexpanded and hyperresonant chest, and intermittent rales and wheezes.

Older Children and Adults

Recurrent infection with RSV after the age of 2 yr most commonly manifests as upper respiratory tract infections or tracheobronchitis. Asymptomatic infections and lower respiratory disease are uncommon in this age group. Typically, symptoms

Table 8
Respiratory Syncytial Virus Infection Control Guidelines

General control measures to prevent nosocomial RSV transmission:
Educate hospital staff about RSV epidemiology, modes of transmission, and means of prevention.
Use contact and droplet isolation for RSV-positive patients including gloves and gown.
Maintain good handwashing procedures following any contact with RSV-infected patients or fomites, even if gloves are used.
Limit visitors. Do not allow visitors with who have symptoms of respiratory infection to visit uninfected pediatric, immunosuppressed, or cardiac patients.
Restrict staff with upper respiratory symptoms from patients at high risk for complications from RSV infection.
Control measures during RSV outbreaks:
Avoid elective admissions for high-risk patients.
Admit young children with symptoms of viral upper respiratory infections to single rooms.
Cohort patients with RSV infection.
Cohort staff to infected or uninfected patients.

Data from refs. *53,58.*

include nasal congestion and cough with a more severe and prolonged course as compared to "colds" caused by other respiratory viruses.

Elderly

RSV appears to be an increasing cause of respiratory disease in this population, especially those in nursing care facilities. During outbreaks, the attack rate ranges from 10% to 40% and accounts for 5–27% of all respiratory tract infections in long-term care facilities. Individuals over the age of 60, typically, present with mild nasal congestion, but fever, anorexia, pneumonia, or bronchitis may develop *(55–57).*

Treatment

The initial concern should be prevention. Interrupting transmission at healthcare facilities is necessary to prevent the spread of infection. Special precautions should be advocated in RSV infected patients during the peak RSV season and, especially, when a hospital outbreak develops. Table 8 lists infection control guidelines.

The mainstay of therapy consists of respiratory support, nutrition, and hydration. The use of antivirals in the treatment of RSV infections remains controversial. Ribavirin is the only antiviral agent licensed for the treatment of RSV infections. Patients undergoing therapy should be placed in negative pressure rooms with frequent air exchanges and scavenging systems to decrease exposure to healthcare providers and to minimize release into the surrounding environment. Ribavirin is dosed at 6 g/300 cc of water over 18 h or 6 g/100 cc of water over 2 h three times a day. Early clinical trials of aerosolized ribavirin therapy suggested some therapeutic benefit; however, interpretation of the results is complicated by the investigators' use of distilled water, a known bronchoconstrictor, as the placebo treatment. A similar study, when conducted using aerosolized saline as the placebo, found no clinical benefit from ribavirin therapy *(59).*

Cohort studies also failed to demonstrate an improved clinical outcome with ribavirin therapy *(60,61).* The Committee on Infectious Diseases of the American Academy of Pediatrics has changed its recommendations on the use of ribavirin to "may be considered" in selected infants and young children at high risk for serious RSV disease *(62);* however most clinicians do not use aerosolized ribavirin because of the limited clinical benefit, cost, and difficulty in administration. Other agents such as bronchodilators (β-agonists and epinephrine) and antiinflammatory agents (cromolyn sodium and budesonide) have demonstrated some clinical improvement, but further studies are required to confirm these findings *(52,53,58).*

Palivizumab is an FDA-approved humanized monoclonal antibody directed against an RSV surface glycoprotein. The recommended dose of palivizumab is 15 mg/kg i.m. every month during the RSV season for those individuals at increased risk of severe RSV infections. Prophylaxis should be individualized based on risk of complications if RSV is acquired.

Initial studies of palivizumab dosed at 15 mg/kg i.m. every month for 5 mo during the peak RSV season demonstrated an overall reduction in RSV-related hospitalizations by 55% with significant reductions in premature infants with chronic lung disease (39%) and premature infants without chronic lung disease (78%). Other significant reductions included number of hospital days (42%), days of oxygen requirement (40%), and incidence of ICU care (57%) *(63,64).* Advantages to the use of palivizumab include intramuscular route of administration, a delay in dosing other vaccines is not required, and palivizumab is not a blood product, and thus carries no risk of transmitting blood-borne pathogens. Palivizumab are not FDA approved for infants with congenital heart disease because of concerns regarding the safety in these individuals.

Key Points

- The viral illnesses of influenza, herpes viruses, varicella/zoster virus, and respiratory syncytial virus are commonly seen in outpatient settings and have substantial morbidity, and, in the case of influenza, mortality associated with them.
- Prevention a key with these viral illnesses. Influenza and varicella are effectively managed through vaccination. Herpes transmission can be prevented through behavioral changes and education. In high-risk individuals, RSV infection can be reduced by immunoprophylaxis.
- Antiviral agents are effectively used to decrease morbidity and mortality for these illnesses. Although resistance to these antiviral agents has been seen, it is currently relatively low.

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5
Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

Frank Romanelli and Claire Pomeroy

CLINICAL DESCRIPTION

In the early 1980s, previously healthy homosexual men began presenting with *Pneumocystis carinii* pneumonia (PCP) and other opportunistic infections. It soon became evident that these men were suffering from immunocompromise brought on by the human immunodeficiency virus (HIV). The virus targets $CD4^+$ cells, resulting in damage to the immune system and leaving infected individuals susceptible to a spectrum of opportunistic infections.

The clinical course of HIV infection differs substantially from individual to individual. Despite this variation it has been possible to document the course of a typical infection. Sexual transmission via the genital mucosa is the most common mode of acquisition of HIV. Following infection, an acute phase ensues involving widespread replication and dissemination of the virus *(1)*. The acute phase may be asymptomatic or may be manifested by constitutional symptoms including fever, weight loss, fatigue, adenopathy, and night sweats. These symptoms may develop within days to weeks of initial exposure. While these symptoms can last from days to weeks, the mean duration is usually 14 d *(1)*. During this phase HIV antibodies may not yet be formed and therefore antibody testing may fail to establish the diagnosis. A patient is considered "HIV-seropositive" when two consecutive HIV enzyme-linked immunosorbent assay (ELISA) antibody tests are positive and confirmation has been attained via a Western blot assay *(2)*.

An asymptomatic phase usually follows the acute phase and is characterized by a reduction in both viral load and symptomology *(1)*. The reduction in viral load is most likely due to a virus-specific immune response. Following this initial drop in viral load, a steady-state setpoint is usually reached. Persons with higher viral load setpoints are more likely to progress to AIDS. Eventually, viral replication exceeds immune response and patients progress to end-stage disease, which is characterized by persistently elevated viral loads and declining $CD4^+$ cell counts. A diagnosis of acquired immunodeficiency syndrome (AIDS) is established by a $CD4^+$ cell count of 200 cells/mm^3 or the presence of specific opportunistic infections *(1)*.

The decline in $CD4^+$ cell counts and other damage to the immune system in HIV-infected individuals makes them susceptible to a number of opportunistic infections.

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Many of these infections are closely correlated with the number of $CD4^+$ cells and degree of immune suppression. Commonly encountered opportunistic infections include PCP, toxoplasmosis, *Mycobacterium avium* complex, candidiasis, cryptococcosis, and cytomegalovirus *(1)*.

The availability of antiretroviral drugs has significantly extended life expectancies of individuals infected with HIV, but drug resistance threatens the efficacy of these regimens. Characterization and delineation of resistance patterns is a critical and ongoing process. The clinical implications and ramifications of resistance on drug selection remains an area of intense research and limited information. Research examining novel antiretroviral agents with increased stability to resistance is underway. Ultimately, it is likely that an effective vaccine will be needed if our goal of HIV eradication is to be attained.

EPIDEMIOLOGY

HIV infection has reached pandemic proportions, with life-spans in some underdeveloped nations significantly shortened as a result of widespread infection. As of the end of 1997, an estimated 30.6 million people worldwide have been living with HIV *(2)*. Twenty nine and one half million of those individuals are adults and 1.1 million are children younger than the age of 15 yr. Approximately 41% of HIV-infected adults are women, and trends indicate that this proportion is growing. Worldwide, heterosexual transmission accounts for about 75% of all infections *(2)*. Among children and infants, perinatal transmission accounts for >90% of infections *(2)*. HIV infection rates in underdeveloped countries far exceed rates in developed nations. It is estimated that in 1997 more than 90% of all new HIV infections occurred in developing countries *(2)*. The high rates of infection and mortality in these countries have significantly affected average life-spans. Lack of education, preventative efforts, and access to affordable antiretroviral medications all contribute significantly to the global spread of HIV.

In the United States, AIDS was the leading cause of death in young men in 1996. Encouragingly, new AIDS cases reported to the Centers for Disease Control (CDC) declined 12% from 1996 to 1997 *(3)*. Deaths from AIDS also fell by 47% from 1996 to 1997. According to the CDC, AIDS is no longer the number one cause of death in American men aged 25–44 *(2,3)*. This decline in disease progression is believed to primarily result from the use of new, potent antiretroviral medications. An estimated 665,357 people were living with AIDS in the United States as of the end of June 30, 1998 *(3)*. Similar to worldwide trends, the number of AIDS cases among women in the United States has steadily increased to 22% since 1985. Caucasians account for the largest percentage of infected Americans at 45%. Men having sex with men (MSM) account for the greatest percentage of cases (45%), followed by injection drug users (22%). Transmission by heterosexual contact, while not accounting for the majority of cases in the US, has steadily increased since 1991 to 17.5%. Unfortunately, while AIDS-related death rates in the United States continue to decline, infection rates remain unchanged *(2)*.

HIV is not transmitted by casual contact *(4)*. Transmission of the virus requires the exchange of specific bodily fluids that contain viral particles *(4)*. Blood and semen have the greatest viral burden and thus carry the highest risk of disease transmission.

The virus itself appears to be highly labile, unable to survive in the environment for more then a few hours. Transmission most commonly occurs when bodily fluids are exchanged during sexual contact *(5).* Anal intercourse, because of its traumatic nature, carries the greatest risk of transmission, followed by vaginal intercourse and receptive oral sex *(5).* When used appropriately, barrier methods such as latex condoms and dental dams have been shown to reduce the risk of transmission from sexual contact. However, it must be emphasized that condoms and other barrier methods do not entirely eliminate risk.

Intrauterine transmission is the most common cause of infant and pediatric HIV infection *(7).* Treatment of mother and baby with zidovudine may reduce the potential for perinatal transmission by up to 67.5%. To reduce the risk of intrauterine transmission, zidovudine should be administered at doses of 100 mg p.o. five times per day at 14–34 wk of gestation, followed by zidovudine 2 mg/kg i.v. load and 1 mg/kg/h during delivery *(6).* The neonate should then be given zidovudine 2 mg/kg p.o. q6h for the first 6 wk of life. Because monotherapy of infected individuals including pregnant women is no longer considered acceptable, many clinicians now advocate treating women with triple highly active antiretroviral therapy. Studies are underway to determine the optimal and most cost-effective drug regimens for prevention of perinatal transmission.

The use of unclean needles by injection drug users is also a common mode of viral transmission. If sterile needles are not available, disinfection of used needles with full stength bleach should be encouraged. The implementation of standard precautions has lowered the incidence of needlesticks within occupational settings. Standard precautions dictate that blood and other high-risk bodily fluids from *all* patients should be considered potentially infectious. Thus, appropriate personal protection equipment (e.g., masks, gowns, gloves) should be employed when caring for all patients in situations where contact with body fluids is anticipated. The risk of contracting HIV from a needlestick is estimated to be 0.32% *(7).* The risk of seroconversion is increased when the source patient has end-stage disease accompanied by a high HIV titer. The use of post-exposure prophylaxis (PEP) appears to reduce the risk of transmission by as much as 79% *(8).* PEP should be offered in all cases of a needlestick from an HIV+ patient *(7).* Current guidelines call for a three-drug regimen to be initiated as soon after the exposure as possible. The three-drug regimen most commonly advocated consists of a 30-d course of: zidovudine 300 mg p.o. b.i.d., lamivudine 150 mg p.o. b.i.d., and indinavir 800 mg p.o. q8h *(9).* Recipients of accidental needlesticks should receive HIV ELISA testing at baseline, then 6 wk, 12 wk, and 6 mo post-exposure *(9).* The increasing frequency of resistant HIV strains has led some experts to advocate tailoring recommendations for PEP based on the sensitivities of the source patient's virus, if known.

ETIOLOGY

HIV exists in two distinct forms, HIV-1 and HIV-2. HIV-2 appears to be a less virulent form of the virus that is usually associated with a slower clinical course. Unfortunately, 99.9% of HIV-infected individuals within the United States are infected with HIV-1 *(10).* HIV has a remarkable capacity for both replication and mutation. HIV produces an estimated 10^{10} new particles daily while generating one mutation per genome per cycle *(11).*

HIV may be further classified as syncytium inducing (SI) or non-syncytium inducing (NSI) *(12).* Syncytia are fusions of cells into large multinucleated cells. This phenomenon has been observed in other viral diseases including herpesvirus infections, measles, parainfluenza, and mumps. It occurs in HIV when infected cells expressing viral proteins bind to other cells expressing $CD4^+$ receptors, such as T lymphocytes. Whether or not a virus is SI depends upon its chemokine receptors. Patients with SI virus appear to have a more rapid disease progression *(13).*

Once HIV is transmitted and gains entry to the bloodstream, it seeks out $CD4^+$ cells through receptor-mediated identification and entry (Fig. 1) *(14).* $CD4^+$ cells, named for their $CD4^+$ receptors, play an integral role in the overall modulation of the immune system. With damage to $CD4^+$ cells, the immune system is rendered dysfunctional. Within the host $CD4^+$ cells, the virus will prepare to manufacture the necessary viral components for replication. HIV is classified as a retrovirus; therefore, its endogenous genetic material is RNA, unlike the human endogenous genetic material, which consists of DNA *(5).* Retroviruses transcribe RNA to DNA then back to RNA; RNA is then eventually translated into viral proteins. The transcription of RNA to DNA is accomplished by a retrovirus-exclusive enzyme known as reverse transcriptase *(14).*

Once HIV has catalyzed the conversion of viral RNA to viral DNA, the DNA must be integrated into human DNA. This is accomplished via the viral enzyme integrase and is a necessary step in the replication cycle because HIV lacks the cellular machinery for the transcription of DNA *(14).* In effect, the virus takes advantage of the host $CD4^+$ cell, which will inadvertently aid in HIV replication by transcribing the integrated piece of viral DNA into viral RNA.

After viral DNA is transcribed and viral RNA is translated, viral proteins are manufactured (Fig. 1). These proteins are polyproteins that require catalytic cleavage by HIV protease enzymes for activation. Upon activation of these proteins, HIV will assemble itself and depart from the host cell *(14).* This new virion will then infect another $CD4^+$ cell and repeat the replication cycle. The processes involved in the release of the new HIV virions result in $CD4^+$ cell death.

As $CD4^+$ cell counts decline (normal 800–1000 cells/mm^3), immune system function is adversely affected, and the patient is at risk for the development of opportunistic infections such as tuberculosis, PCP, cytomegalovirus, and toxoplasmosis *(14).* Death is usually not a result of HIV disease itself but rather occurs from the secondary opportunistic infections or malignancies that develop.

TREATMENT

Overview

Consensus guidelines are available to guide therapy of HIV-infected individuals *(15,16).* Currently three different classes of antiretroviral medications are available for use (Table 1). Each of these medications acts to inhibit at least one key step in the HIV replication cycle. Zidovudine was the first drug indicated for the management of HIV infection. Subsequently, many agents have been added to the HIV armamentarium *(1).* Concentrated efforts by virologists and clinicians have made HIV pharmacotherapy an area of intense development and research. Management guidelines and

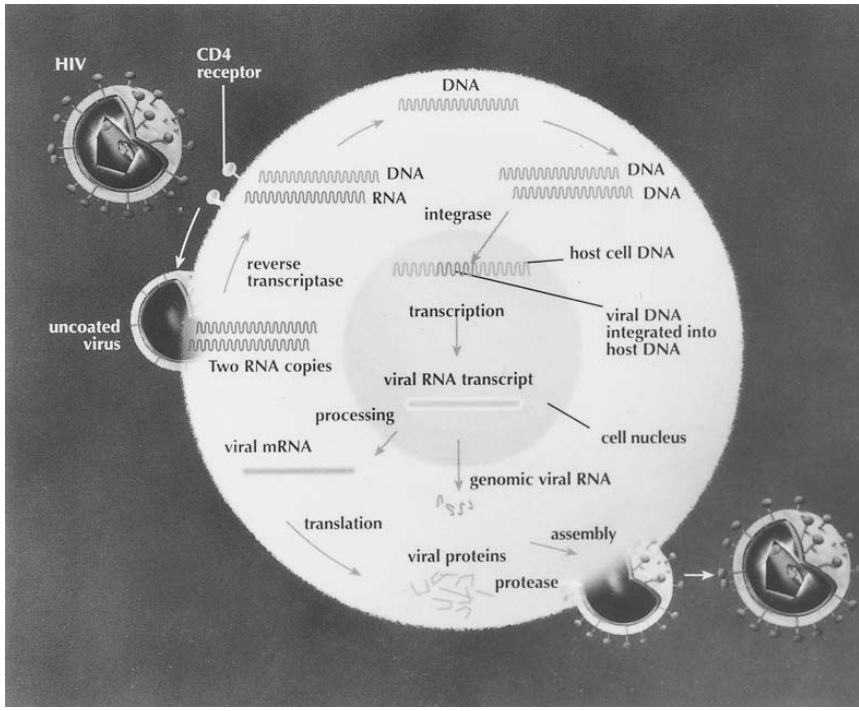

Fig. 1 Replication cycle of HIV-1. From: HIV Resistance and Implications for Therapy. Reproduced with special permission from Medicom, Inc. © 1998.

available agents are constantly changing. Clinicians managing infected individuals must recognize that HIV pharmacotherapy is a rapidly evolving area and should always consult the most recent data available. Treatment decisions must be individualized—taking into account guidelines, patient preference, cost, adverse effects, and risk of resistance.

Initial choice of therapy should include three antiretroviral medications, most often two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) *(15),* or two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Combinations of two NRTIs are also listed as acceptable in many guidelines. Other combinations, including dual PI containing regimens are under active investigation. Monotherapy is unacceptable secondary to the rapid development of resistance *(15).* The first class of antiretrovirals to be introduced was the NRTIs. NRTIs bind to reverse transcriptase and become incorporated into viral DNA, causing termination of chain elongation and DNA synthesis. The NNRTIs act in a similar fashion to inhibit viral DNA synthesis but are distinct in that they are not incorporated into the viral DNA chain. The PI, which are considered to be the most potent class of antiretroviral medications, act to prevent the proteolytic activation of HIV polyproteins by binding to and

Table 1
Nucleoside Reverse Transcriptase Inhibitors
Bind to and inhibit the enzyme responsible for the conversion of viral RNA to viral DNA.

Generic	Abbreviation	Dosing	Trade Name	Adverse Effects
Zidovudine	AZT	200 mg t.i.d. 300 mg b.i.d.	(Retrovir®)	Marrow suppression
Didanosine	ddI	<60 kg: 125 mg b.i.d. >60 kg: 200 mg b.i.d.	(Videx®)	Pancreatitis, peripheral neuropathy
Zalcitabine	ddC	0.75 mg t.i.d.	(Hivid®)	Pancreatitis, peripheral neuropathy
Stavudine	d4T	40 mg b.i.d.	(Zerit®)	Peripheral neuropathy
Lamivudine	3TC	150 mg b.i.d.	(Epivir®)	Peripheral neuropathy
Abacavir	ABC	300 mg b.i.d.	(Ziagen®)	Hypersensitivity reaction
Zidovudine Lamivudine	AZT 3TC	One capsule b.i.d.	(Combivir®)	Marrow suppression, peripheral neuropathy, pancreatitis

Non-nucleoside Reverse Transcriptase Inhibitors
Bind to and inhibit reverse transcriptase enzyme; structurally distinct from NRTIs.

Generic	Dosing	Trade Name	Adverse Effects
Nevirapine	200 mg qdX2 wk, then 200 mg b.i.d.	(Viramune®)	Rash, diarrhea
Delavirdine	400 mg t.i.d.	(Rescriptor®)	Rash, headache
Efavirenz	600 mg qhs	(Sustiva®)	Rash, CNS disengagement

Protease Inhibitors
Bind to and inhibit protease enzyme. Protease enzyme normally cleaves and activates HIV proteins.

Generic	Dosing	Trade Name	Adverse Effects
Saquinavir (hard gel)	600 mg t.i.d.	(Invirase®)	Nausea, vomiting, diarrhea
Saquinavir (soft gel)	1200 mg t.i.d.	(Fortavase®)	Nausea, vomiting, diarrhea
Ritonavir	600 mg b.i.d.	(Norvir®)	Drug interactions, GI distress, perioral tingling
Indinavir	800 mg q8h	(Crixivan®)	Nephrolithiasis, increased bilirubin
Nelfinavir	750 mg t.i.d.	(Viracept®)	Diarrhea, nausea
Amprenavir	1200 mg b.i.d.	(Agenerase®)	Nausea, rash

disabling viral proteases. The use of PIs requires vigilant adherence; therefore, certain patients may not be candidates for their use.

$CD4^+$ cell counts and viral load values are used to guide decisions regarding when to initiate as well as alter therapy *(15).* Viral load testing is a measure of viral RNA within the bloodstream and is a method for the quantification of viral burden. Two methods of viral load testing are available, polymerase chain reaction (PCR) and branched chain DNA (b-DNA) *(18–20).* Because these two methods can produce varying results, clinicians should compare only values derived from the same testing method, that is b-DNA or PCR. Typical viral load assays cannot detect viral RNA below 400 copies/mL, in which case the results will be reported as "undetectable." Newer ultrasensitive assays whose lower limit of detection is 50 copies/mL are becoming widely available *(19).*

Generally, therapy should be initiated when the $CD4^+$ cell count is < 500 cells/mm^3 or when viral load is in the range of 5000–10,000 copies/mL *(15).* Recently some practitioners have suggested initiating therapy as soon as possible after infection to lower the initial viral setpoint (which has been linked to prognosis), delay disease progression, and prevent opportunities for the emergence of resistance.

The goal of therapy is to attain and maintain an undetectable viral load. Studies have demonstrated that when viral load is maintained at undetectable levels the likelihood for the development of resistance is reduced *(20).* An undetectable viral load has also been associated with stronger immune system preservation and reconstitution *(20).* Viral load should be measured 30 d after the initiation of therapy and every 90 d thereafter. Therapy should be adjusted if an undetectable viral load is not achieved, if a previously undetectable viral load increases to detectable levels (confirmed on repeat testing), or if a patient with a previously controlled viral load has an increase in viral load of at least 0.5 $\log_{10}$.

In designing antiretroviral drug regimens, clinicians should always consider drug–drug interactions. Interactions involving increased metabolism of antiretrovirals may result in subtherapeutic drug concentrations and treatment failure as a result of the development of resistance. Management of drug interactions is a particular challenge, as patients may be prescribed multiple medications for both HIV as well as opportunistic infections. Appropriate references should always be consulted to identify and evaluate drug interactions in this population *(22).*

Subsequent to the initiation of antiretrovirals, viral loads should be closely monitored. In cases of treatment failure, when a previously undetectable viral load has increased or viral load is unresponsive to therapy, patients should be started on three new antiretroviral medications *(15).* Ideally, the patient should be treatment naïve to the three new medications selected. Addition of a fourth drug to a failing regimen is inadequate and often yields the same results as monotherapy. In cases of drug toxicity or adverse effects, it is appropriate to substitute one drug from the same class without altering the other components of the regimen *(15).*

The success of combination antiretroviral therapy is highly dependent on patient adherence *(21,24).* Vigilant adherence is the best protection against the development of resistance. Adherence is particularly critical among those patients using protease inhibitors. The rapid development of resistance to these drugs and the high incidence of intraclass cross-resistance makes them particularly susceptible to treatment failure in nonadherent patients *(24).* Adherence is a challenge for many HIV+ patients because

of various factors including high pill burdens, cost, adverse effects, and lifestyle modifications. When counseling patients, clinicians should ensure that the topic of adherence is stressed. Time should be devoted to ensuring a clear understanding of HIV disease and specific treatment goals.

Many patients who are placed on three drug antiretroviral regimens achieve and maintain undetectable viral load values for prolonged periods of time. These patients will, however, continue to harbor the virus within lymph nodes and central nervous system (CNS) tissue *(26).* Transmission of the virus is still possible and patients should be advised to use latex condoms and other methods of barrier protection. The ability to suppress viral replication over a long period of time has raised the issue of antiretroviral medication discontinuation. While sustained undetectable viral loads have been achieved in large numbers of patients, when antiretrovirals are withdrawn, previously undetectable virions begin to once again actively replicate *(25).* Until further trials are completed, it would be premature to discontinue antiretroviral medications in response to sustained undetectable viral load values.

The search for new and effective antiretrovirals continues. Emphasis has been placed on the development of medications with simplified dosing regimens and reduced pill burdens. Existing medications are also being combined in various ways to simplify dosing regimens. These combinations often take advantage of drug interactions. For instance, because of the inhibitory effects of ritonavir on the metabolism of saquinavir, the two drugs have been combined in a b.i.d. dosing regimen *(23).* Currently this regimen is considered salvage therapy and is generally utilized only when conventional therapeutic interventions have been exhausted.

A novel approach to the inhibition of viral replication involves the use of the chemotherapeutic agent hydroxyurea *(27).* Hydroxyurea is a ribonucleotide reductase inhibitor that may have some efficacy in reducing viral replication by potentiating the mechanism of action of the NRTIs, particularly didanosine. While considered salvage therapy, if hydroxyurea is employed it should be combined with didanosine. Neutropenia has been a major dose-limiting adverse effect of hydroxyurea. This effect is of particular concern in HIV+ persons who may already have baseline immune dysfunction. In patients using hydroxyurea, complete blood counts should be closely and routinely monitored. The neutropenia that may develop is usually self-limiting and resolves upon discontinuation of the drug.

Impact of Resistance

Both the magnitude and duration of antiretroviral efficacy are limited by the development of resistance. In terms of HIV, resistance can be defined as any change that improves viral replication in the presence of an inhibitor such as antiretroviral medication. For resistance to occur, the specific antiretroviral target enzyme structure must change, yet retain its normal function. Resistance to antiretrovirals is quick to develop secondary to the intrinsically error-prone replication of HIV. The virus commits between 0.2 and 1 point mutation with each replication cycle *(10).* Unlike humans, HIV has no mechanism to correct genetic errors associated with the process of replication. The high rate of replication of HIV also acts to potentiate this process. With an average turnover rate of 10^9 virions per day and a mutation rate of 10^{-4}, every possible point mutation will occur up to 10^5 times per day *(10).*

Point mutations result in alterations of the nucleotide sequence of DNA at a specific codon *(28).* Altered codons result in the substitution of one amino acid for another during translation. The end result will be the substitution of various amino acids, which changes the protein chains of critical HIV enzymes such as reverse transcriptase and protease. These altered enzymes may or may not be functional. Those enzymes that perserve their function will likely be resistant to certain antiretrovirals secondary to alterations in their chemical structure. Several amino acid variations that are associated with resistance to specific antiretrovirals have been described *(28).*

As HIV replicates and mutations develop, many species of the same virus will evolve. Each of these species will vary to some degree from the initial viral inoculum (wild-type). When antiretroviral drug pressure is applied, preexisting resistant strains continue to replicate and rapidly become the predominant strain. Certain antiretrovirals require only single mutations to occur for resistance to develop, while others require more than one. In situations where viral load is not optimally suppressed, a greater propensity for the emergence of resistance exists owing to ongoing viral evolution *(31).* Although it appears that the transmission of resistant virus has been fairly uncommon, much concern has been raised as antiretroviral use becomes more widespread and resistant viruses enter the population *(28).*

Resistance has been classified as being either genotypic or phenotypic. Genotypic resistance refers to the specific sequencing of nucleotides that compromise codons *(28).* The genotype sequence of specific strains can be compared to the reference wild-type virus (initial viral inoculum). Changes from the wild-type can be described as a change in an amino acid at a specific codon of the protein. For example, a change from ATG to GTG at codon 184 would be reported as a change from methionine to valine at residue 184, or M184V. Phenotypic resistance refers to the ability of a specific viral strain to grow in vitro in the presence of a specific inhibitor when compared to the wild-type virus. In vitro susceptibility is typically expressed as either IC_{50} or IC_{90} *(28).* This refers to the drug concentration required to inhibit viral replication by 50% or 90%, respectively. For example, if a wild-type virus has an IC_{50} of 100 n*M* for a particular drug and a test strain has an IC_{50} of 1000 n*M,* the test strain has 10-fold resistance to that particular drug.

Clinically, resistance is defined as an increase in viral load in a patient with previously undetectable levels. Resistance may also be manifested as a failure to achieve undetectable viral load values after an adequate trial of antiretroviral medications. Adherence must always be considered, as decreased adherence will result in failure to control the viral loads. Vaccinations and secondary infections (e.g., sinusitis, pneumonia) may also elevate viral load and therefore an increase in viral load may not necessarily indicate the presence of resistance. Clinical resistance may be substantiated by the existence in vitro of phenotypic and/or genotypic resistance.

Resistance to NRTIs and NNRTIs develops from mutations involving the genes that encode for the reverse transcriptase enzyme. Within 2 yr of the introduction of zidovudine in 1987, fully resistant strains were being isolated from patients who had been on prolonged therapy *(29).* Patients receiving zidovudine therapy can be expected to develop zidovudine-resistant strains as soon as 6 mo following the initiation of therapy *(29–31).* The prevalence of resistance increases over time with 50% of treated patients having zidovudine-resistant strains after 2 yr *(31).* Lower baseline $CD4^+$ cell counts (< 50 cells/mm^3) have been correlated with the increased emergence of resistance

(29–31). The presence of SI virus also predisposes to the more rapid development of zidovudine resistance *(31).*

Resistance to zidovudine is particularly concerning, as it has been shown to be an independent predictor of clinical failure. In the AIDS Clinical Trial Group (ACTG) 116B/117 trial, high-level phenotypic resistance to zidovudine at baseline was associated with accelerated disease and greater progression to death, independent of $CD4^+$ cell count and viral load *(32).* The most common genotypes associated with high-level zidovudine resistance and clinical failure are M41L, T215Y/F, D67N, and K70R *(30–32).*

HIV-1 rapidly selects for resistance to lamivudine. The most common genotypic mutation is M184V/I, which confers approx 1000-fold decreased susceptibility to lamivudine *(33,34).* The resistant strains begin to develop as soon as 2 wk following the initiation of therapy, and by 3 mo, > 95% of patients will carry the resistant mutation *(35).* Combination therapy with zidovudine does not delay the emergence of resistance to lamivudine, but the M184V/I mutation may confer increased susceptibility to zidovudine *(36).* Hence, in clinical practice these two agents are often used in combination.

Both didanosine and zalcitabine appear to have rather stable resistance profiles *(29–31).* Most documented mutations involving these two agents have resulted in only a five to tenfold increase in resistance. These findings may be related to the fact that didanosine and zalcitabine are more closely structurally related to natural nucleosides than are zidovudine or lamivudine *(31).* The use of didanosine or zalcitabine in combination with zidovudine has been shown to suppress many of the mutations associated with monotherapy but may also select for the development of novel and possibly more compromising mutations *(30).*

The existence of selective resistance to stavudine has been documented, although specific resistance patterns have been difficult to characterize *(31).* In vivo and in vitro data have been difficult to compare and are often contradictory. Most patients with documented stavudine resistance demonstrate no common genetic basis to explain the decreased susceptibility.

The newest agent to join the class of NRTIs is abacavir. Although it is premature to predict the resistance patterns of this agent secondary to limited use, there appears to be no in vitro cross-resistance with zidovudine. In vitro data have shown that most mutations to abacavir result in only a three- to ten-fold increase in resistance *(37).* The agent does select for mutations at 184V, raising concerns about its use in patients who are lamivudine experienced *(31,37).* Initial data indicate that the medication may be best used following combination therapy involving zidovudine plus didanosine or zalcitabine. The therapeutic role for this agent will become evident as its use becomes more widespread.

Despite the recent introduction of the NNRTIs, resistance to this class has been fairly quick to develop. This may be due to the number of possible single point mutations that can confer resistance to nevirapine and delaviradine *(32).* Significant cross-resistance among members of this class has also been documented. Efavirenz is the newest of the NNRTIs and the major route of resistance is believed to be by the K103N mutation *(38).* This mutation results in an approx 19-fold reduction in susceptibility.

Since their introduction the PIs have been recognized as a highly potent class of antiretrovirals. They are able to suppress viral load to a greater extent and duration than are the reverse transcriptase inhibitors *(25).* Their use has resulted in dramatic clinical

responses. However, resistance has been the major limitation of PIs. Protease enzyme is able to accommodate multiple mutations while maintaining functionality. More than 25 different codons have been implicated in the development of resistance to PIs. There also appears to be a great deal of cross-resistance among members of this class owing to overlap in mutational patterns *(39).* Unlike the NRTIs and the NNRTIs, PIs usually require the accumulation of multiple mutations at different sites to confer resistance. Studies examining the utility of dose escalation of PIs such as indinavir and ritonavir have identified a greater inclination toward the development of resistance *(40).* This highlights the importance of achieving adequate drug levels and vigilant adherence when employing these agents *(40).*

Although saquinavir was the first PI to be introduced in the United States, poor bioavailability (4% Invirase®, 12% Fortavase®) has limited its use in antiretroviral regimens. Resistance to saquinavir does not appear to develop rapidly, which may in part be due to the drug's poor bioavailability *(41).* Resistance is most commonly a result of one of two mutations associated with the protease gene (G48V, L90M) *(42,43).* The occurrence of both mutations is rare but when present the virus can be expected to be 100 times less susceptible.

Ritonavir has an improved bioavailability profile compared to saquinavir. Unfortunately, the drug is a potent inhibitor of the cytochrome P-450 system and has multiple serious drug interactions *(22).* During monotherapy, resistance to ritonavir is associated with multiple mutations, although those at codon 82 appear critical to the development of resistance *(44).*

Because of better bioavailability and fewer drug interactions, indinavir has been a popular component of many antiretroviral drug regimens. Like ritonavir, indinavir requires multiple mutations to confer resistance. The most common mutations seen in combination are at codons 82 (V82A) and 46 (M461 or M46L) *(45,46).* Because ritonavir and indinavir share the same key mutation at codon 82, indinavir-resistant strains may be expected to be cross-resistant to ritonavir. Resistance to indinavir has also been correlated with cross-resistance to saquinavir and nelfinavir.

Nelfinavir demonstrates good bioavailability with few drug interactions, and like indinavir is a common component of many antiretroviral drug regimens. Similar to the other PIs, nelfinavir requires multiple mutations to confer resistance. Nelfinavir may possess a distinct mutational pattern in that codon 30 (D30N), not codon 82, appears to be the initial and most critical mutation *(47,48).* This may reduce cross-resistance and afford some advantage in patients who have previously failed on other PIs. More data are necessary to confirm this possibility.

Amprenavir was recently FDA approved and is the newest drug to join the class of PIs. Although conflicting data have been reported, amprenavir appears to have a distinct mutation profile when compared to the other PIs *(49).* Preliminary clinical data did indicate that cross-resistance was possible *(50).* Until more widespread use of this agent is seen in practice, it would be premature to predict exact resistance patterns. Larger trials will need to be conducted to determine the extent of cross-resistance and the role of this novel PI in clinical practice.

The most evident implication of the emergence of resistance on clinical practice is the need for patients to be vigilantly adherent with their prescribed drug regimens. Adherence and maximal viral suppression reduce the likelihood for the emergence of

resistance and slow overall disease progression. In a trial examining the effects of nonadherence in a triple regimen consisting of didanosine, zidovudine, and nevirapine, nonadherence to didanosine led to the emergence of resistance to both zidovudine and nevirapine, as well as increased viral load values and disease progression *(52)*.

Therapeutic failures secondary to nonadherence and the eventual development of resistance are common in the HIV+ population. Intensive counseling on the importance of adherence should be provided to all patients who have been prescribed antiretroviral therapy on an ongoing basis. When considering the initiation of antiretroviral therapy, the patient should be counseled on the realities and importance of adherence. The selection of specific antiretrovirals should be made based upon the likely level of adherence of the patient and the associated lifestyle changes.

It is not yet possible to determine the exact role of drug resistance testing in clinical practice. It does seem clear that testing is a better predictor of drug failure than of drug success *(53)*. Most clinicians would currently consider drug resistance testing to be an adjunct to, rather than a stand-alone guide for decision making, but the acknowledgement of an important role for resistance testing is growing. Several genotypic and phenotypic assays are available or in development *(51)*. Clinicians should be aware of the utility as well as advantages/disadvantages of both techniques (Table 2). Suggested guidelines for the use of testing have recently been issued *(54)*.

Genotypic testing attempts to define changes in the viral genome coding for the reverse transcriptase or protease enzyme, so that mutations that have been linked to the development of resistance can be identified. The first step in this process involves the amplification of RNA or DNA fragments that correspond to the genes encoding for the reverse transcriptase or protease enzyme. Amplification produces a sufficient number of fragments for testing *(52,53)*. Generally, plasma samples must contain at least 1000 copies/mL for accurate results. Genotypic testing is relatively available in most academic laboratory settings. Testing does not require a high level of technical ability and yields rapid results, usually within days. Another advantage of this testing technique over phenotyping is that genetic mutations usually precede phenotypic changes. However, genotypic testing is an indirect measure and may not always correlate with the phenotypic in vivo response. Test results should always be interpreted by an expert in genotyping who can help predict cross-resistance and the impact of specific mutations on phenotypic response.

Phenotypic testing is a measure of the 50% or 90% inhibitory concentration of a drug (IC_{50} or IC_{90}) in vitro *(52,53)*. Testing is conducted by infecting test cells with the viral inoculum from a specific patient. Those cells are then exposed to varying concentrations of the available antiretroviral medications. The ability of HIV to grow in the presence of given antiretrovirals is then compared to standard viral strains which are considered to be susceptible to the particular agent being tested. Unlike genotyping, phenotyping is a direct measure of susceptibility and uses more familiar parameters (IC_{50} or IC_{90}) *(52)*. The clinical significance of specific IC_{50} and IC_{90} values has not yet been established. Phenotyping is technically demanding and not as readily available as genotyping; therefore a longer time to obtain results should be expected (weeks). Another limitation to this technique is that only the dominant wild-type virus will be assayed. Minor species or mutations in progress will not be analyzed.

Table 2
Comparison of Genotypic and Phenotypic Resistance Assays

	Relative Advantages	Relative Limitations
Genotypic	Ease of availability Shorter time to results (days) Less technically demanding Mutations will likely precede phenotypic resistance Less costly when compared to phenotyping	Indirect measure of susceptibility May not correlate directly with phenotype Expert interpretation required Insensitive for detecting minor species Reliance upon known mutations in mapped areas of the HIV genome Lack of laboratory standardization
Phenotypic	Direct measure of susceptibility More familiar reporting results (IC_{50} or IC_{90})	Limited availability Longer time to results (weeks) Technically demanding Insensitive for detecting minor species Clinically significant breakpoints undefined Lack of laboratory standardization Costly

Genotypic or phenotypic testing for drug resistance before the initiation of antiretroviral therapy in treatment naïve patients cannot be routinely recommended at this time because of testing limitations and cost *(52).* However, the growing recognition of primary acquisition of resistant viruses, especially in certain parts of the United States, has led some experts to consider resistance testing prior to starting therapy in treatment-naive patients. Decisions regarding the initiation of therapy should always be made based upon patient-specific factors such as viral load, $CD4^+$ cell count, and clinical status. Resistance testing should never delay the initiation of post-exposure prophylaxis in cases of occupational or nonoccupational HIV exposures.

Viral resistance has been linked to treatment failures, but it would be premature to advocate the routine use of resistance testing as a parameter for recommending alterations in existing antiretroviral therapy. Antiretroviral therapy should be changed when a previously undetectable viral load value has increased, and with a concurrent assessment of other factors such as vaccinations, illnesses, and adherence. Selection of new antiretroviral agents should be based on cross-resistance data available in the literature so that therapy is maximized. Until controlled trials provide more insights into use of testing and a consensus is reached on interpretation, clinicians should continue to rely on viral load and $CD4^+$ cell counts to guide most therapy decisions.

The initial excitement that heralded the advent of antiretrovirals has been tempered by the emergence of resistance. HIV has demonstrated a tremendous capacity to mutate and evolve, making it a constantly moving target. Resistance continues to be the greatest impediment to the efficacy of the antiretrovirals. Trials are being conducted to discern the clinical implications of specific resistance patterns. Until a vaccine is developed, studies must continue to explore the clinical utility of genotypic and phenotypic testing. In the meantime, clinicians should rely on validated assays, ensure

vigilant adherence, and use available resistance data to optimize antiretroviral drug selection.

Key Points

- Effective treatment of HIV with potent highly active antiretroviral therapy decreases the likelihood of selection of resistant virions.
- Protease inhibitors require strict adherence to avoid selection of resistant mutants—alternate regimens should be considered in nonadherent patients.
- Antiretroviral resistance testing will undoubtedly play an increasing role in guiding the choice of antiretroviral therapy.
- Ongoing trials continue to study the clinical implications of specific resistance patterns and future utility of genotypic and phenotypic testing. In the meantime, clinicians should rely on validated assays, encourage strict adherence, and use available resistance data to optimize antiretroviral drug selection.

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6
Fungal Infections

Claire Pomeroy and Norman L. Goodman

INTRODUCTION

Fungal infections are an increasingly important cause of morbidity and mortality, especially among the growing numbers of immunocompromised patients. Until recently, the armamentarium of drugs available to treat these frequently life-threatening diseases was extremely limited. Although the discovery of the azole drugs has significantly increased therapeutic options, additional approaches are still needed—agents currently under study allow considerable optimism for the future. Unfortunately, as with antibacterial drugs, the expanding use of antifungal therapies has led to the emergence of resistant organisms *(1).* Selection of mutants resistant to the azole drugs and even to amphotericin B, as well as the emergence of microbes with intrinsic resistance to available antifungal therapies, raise imposing challenges. Clinicians should be aware of the appropriate management of fungal infections, including recommended empiric therapies, indications for susceptibility testing, and options for treatment of resistant pathogens.

ORGANISMS

The classification of fungi can be quite confusing, especially when toxonomic debates continue among mycologists. For example, the recent reclassification of *Pneumocystis carinii* as a fungus has caused considerable stir. It is most important to recognize that fungi can be categorized as either yeasts or molds. Yeasts are typically round in shape and reproduce by budding, whereas molds are typically composed of tubular structures called hyphae and grow by extension. Many human pathogens are dimorphic fungi, so called because they are yeasts or yeastlike in the human body, but grow as molds outside the body. Table 1 lists the major fungal pathogens.

Candida Species

Candida organisms are yeasts, and several species cause human disease. *Candida albicans* accounts for the majority of human disease, and is responsible for mucocutaneous disease (thrush, vaginitis), as well as invasive disease. However, other *Candida* species are being recognized as important pathogens. *Candida tropicalis* is responsible for up to one fourth of systemic candidiasis and may be more virulent than *C. albicans* in immunocompromised patients. *Candida krusei* and *Candida glabrata* (formerly

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Table 1
Major Fungal Pathogens

Category	Disease	Usual Pathogens
Classic fungal infections	Aspergillosis	*Aspergillus fumigatus,* other *Aspergillus* spp.
	Candidiasis	*Candida albicans,* other *Candida* spp.
	Cryptococcosis	*Cryptococcus neoformans*
Endemic fungal infections	Sporotrichosis	*Sporothrix schenkii*
	Histoplasmosis	*Histoplasma capsulatum*
	Blastomycosis	*Blastomyces dermatitidis*
	Coccidioidomycosis	*Coccidioides immitis*
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
	Penicilliosis	*Penicillium marneffii*
Other invasive fungal infections	Zygomycosis	*Rhizopus arrhizus (oryzae),* other *Rhizopus* spp.; *Absidia* spp., *Cunninghamella* spp., *Mucor* spp., others
	Hyalohyphomycosis	*Fusarium* spp., *Paecilomyces* spp., *Trichoderma* spp.; *Acremonium* spp., *Geotrichum* spp., *Scopulariopsis* spp.
	Phaeohyphomycosis	*Bipolaris* spp., *Exophilia* spp.; *Alternaria* spp., *Curvularia* spp., *Exserohilum* spp., *Phialophora* spp., *Scedosporium* spp.
	Miscellaneous	*Pneumocystis carinii, Pseudallescheria boydii, Malassezia furfur, Trichosporon beigelii, Saccharomyces cerevisiae*
Other usually noninvasive fungal infections	Chromomycosis	Various fungi
	Mycetoma (Madura foot)	Various fungi
	Dermatophytes	*Trichophyton* spp., *Microsporum* spp., Epidermophyton floccosum

Torulopsis glabrata) were quite uncommon in the past, but are observed now more frequently, especially in patients with hematologic malignancies and recipients of bone marrow/stem cell transplants *(2).* Both of these organisms may demonstrate resistance to fluconazole and other azole drugs. *Candida parapsilosis* may cause disease in neonates, oncology patients, and individuals in intensive care units, sometimes due to exogenous acquisition from indwelling catheters or other invasive devices *(3).* A feared emerging pathogen is *Candida lusitaniae,* owing to its inherent resistance to amphotericin B.

Aspergillus Species

These molds are found throughout the environment and can cause serious disease, especially among immunocompromised patients. *Aspergillus fumigatus* and *Aspergillus flavus* are the most frequent pathogens in humans, but a variety of other species can cause clinical disease.

Cryptococcus

The only species of *Cryptococcus* that causes major disease in humans is *Cryptococcus neoformans.* This yeast is ubiquitous in the environment and has emerged as an important cause of infection, especially meningitis in human immunodeficiency virus (HIV)-infected patients.

Endemic Fungi

Endemic fungi are responsible for a large burden of disease. In the United States, *Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis,* and *Sporothrix schenckii* are important pathogens. In other countries, *Paracoccidioides basiliensis* and *Penicillium marneffii* are endemic, the latter emerging as a major opportunistic pathogen among acquired immunodeficiency syndrome (AIDS) patients.

Other Fungi Causing Invasive Disease

A number of *Zygomycetes,* molds in the order Mucorales, including *Rhizopus, Absidia,* and *Mucor,* can cause zygomycosis. These subcutaneous or deep tissue fungal infections occur predominantly in immunocompromised patients, especially neutropenic individuals, patients treated with steroids, and those with HIV or transplants. Rhinocerebral mucormycosis classically occurs in patients with poorly controlled diabetes. *Rhizopus arrhizus (oryzae)* causes 60% of all cases and 90% of rhinocerebral infections; *Rhizopus microsporus* is the second most common pathogen.

Hyalohyphomycosis refers to disease caused by a number of different fungi with hyaline, septate, branched hyphae. Both noninvasive and invasive infections can occur in immunocompromised hosts. The most common causative organisms are *Fusarium* species and *Paecilomyces* spp. A number of other agents have been described, including *Trichoderma* spp. These emerging infections are of particular concern as some, such as *Paecilomyces* spp., are resistant to amphotericin B.

Several different dematiaceous, that is, darkly pigmented, fungi cause a group of infections referred to as phaeohyphomycoses. Localized or disseminated disease can occur in immunocompromised patients. *Bipolaris* spp. and *Exophilia* spp. are the most common pathogens. Various species have demonstrated resistance to antifungal therapy including *Scedosporium prolificans,* which is resistant to all known antifungal drugs.

Other important fungi include *Pneumocystis carinii,* the causative agent of *P. carinii* pneumonia; *Pseudallescheria boydii,* an important cause of disease in immunocompromised patients that may be resistant to amphotericin; *Malassezia furfur,* which can be transmitted via fatty acid containing hyperalimentation solutions and cause sepsis in neutropenic patients; *Trichosporon beigelii,* a cause of invasive disease in severely immunocompromised individuals; and *Saccharomyces cerevisiae* or Brewer's yeast, a cause of vulvovaginitis, as well as disseminated disease in immunocompromised patients.

Other, Usually Noninvasive, Fungi

A multitude of fungi can cause chromomycosis, a chronic fungal infection usually occurring on an extremity that remains localized within the cutaneous or subcutaneous layers. *Fonsecaea pedrosi* is the most common isolate throughout the world. A variety of other fungi can cause mycetoma, also known as Madura foot, a localized, destructive infection of the skin, fascia, bone, and muscle. The most frequent cause of the disease in the United States is *P. boydii* while *Madurella mycetomatis* predominates in Africa and India. Fungal mycetoma must be distinguished from comparable disease caused by aerobic actinomycetes. Molds, including *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton floccosum,* are the causes of dermatophytosis. Classification schemes for these fungi are somewhat controversial, but there are approx 39 species that cause human disease. A fungus of special note is *M. alassezia furfur,* the cause of pityriasis or tinea versicolor, which also causes invasive disease in immunocompromised patients.

RESISTANCE

A major concern is the emergence of fungal strains resistant to antifungal drugs *(4).* (*see* Table 3). While not yet as widespread as antibacterial resistance, antifungal resistance is noteworthy because of the limited options available for treating these infections and the frequently life-threatening nature of these illnesses. Antifungal resistance can be either intrinsic or acquired. Intrinsic resistance occurs regardless of previous drug exposure. For example, *Aspergillus* spp. and *C. krusei* are never inhibited by fluconazole and thus exhibit intrinsic resistance. Fungi that are intrinsically resistant to antifungal therapies may be selected in patients receiving antifungal drugs, for example, the selection of *C. krusei* in patients on azole prophylaxis *(5).* Acquired resistance occurs when the organisms mutate to become resistant to a drug that the patient has been taking. The emergence of fluconazole-resistant *C. albicans* in HIV-infected patients receiving azole prophylaxis is an example that has generated concern. Fortunately, unlike antibacterial resistance, fungi do not appear to transfer resistance genes from one species to another, presumably predicting a slower rise in resistant fungi than has been observed with bacteria.

Azole Resistance

Most *C. albicans* are sensitive to fluconazole and other azole drugs *(6,7).* However, the growing use of these drugs for treatment and prophylaxis, especially in AIDS patients and on transplant units, has led to emergence of isolates resistant to azole drugs. Recent reports suggest that nearly one third of patients with advanced AIDS can develop azole-resistant *Candida* infection *(8).* Most often, the *C. albicans* demonstrates progressively rising minimum inhibitory concentrations (MICs) to fluconazole over time, becoming more resistant the longer the patient has taken the drug *(9).* Case reports of acquisition of fluconazole-resistant strains by HIV-infected individuals have also appeared. Furthermore, HIV-infected patients receiving chronic fluconazole therapy may develop infections with other *Candida* species that are characterized by relative resistance to azole drugs, especially *C. glabrata* and *C. krusei.*

Additional cases of fluconazole-resistant *Candida* species have been reported in neonates, recipients of prosthetic devices, and ICU patients with monitoring devices. In

Table 2
Mechanisms of Action and Mechanisms of Antifungal Resistance

Drug	Mechanisms of Action	Mechanisms of Resistance
Amphotericin B	• Binds to ergosterol in fungal membrane → pore formation → leakage of intracellular contents • ?–Oxidative damage	• Altered ergosterol content in fungal membrane • Altered β-1, 3-glycan composition in fungal membrane → decreased drug permeability
Azoles	• Binding to the enzyme lanosterol 14α-demethylase which is required for ergosterol synthesis • Azole-induced changes in cell membrane also interfere with other membrane-bound enzymes such as those required for chitin synthesis • Interference with other enzymes required for synthesis of ergosterol surrogates	• Altered 14α-demethylase production or affinity for fluconazole • Altered ergosterol content in fungal membrane • Incorporation of alternate sterols in fungal membrane. • Decreased permeability of fungal membrane → reduced intracellular accumulation of drug • Drug efflux pumps

some cases, these patients had never received azole therapy, suggesting acquisition of the resistant strain rather than selection of a resistant mutant. Rarely, immunocompetent individuals may develop fluconazole-resistant candidiasis *(10).* A recent report describes a patient with diabetes and a history of intravenous drug abuse (IVDA) who developed community-acquired fungemia due to a multiple azole resistant strain of *C. tropicalis (11).* Depending on the resistance mechanism, fungi that became resistant to fluconazole may or may not demonstrate cross-resistance to other azole drugs.

Less frequently, other fungi may be resistant to fluconazole and/or other azole drugs. Fluconazole-resistant isolates of *H. capsulatum* and *C. neoformans* have been reported. Most of these have been in patients with AIDS who were receiving fluconazole prophylaxis. A fluconazole-resistant *C. neoformans* was isolated from an immunocompetent patient without prior exposure to azole drugs *(12).* Recently, itraconazole-resistant isolates of *A. fumigatus* were documented.

The mechanisms responsible for azole resistance are an active area of investigation (Table 2). The major mechanism of action of azole drugs appears to be interference with the enzyme 14α-demethylase which is required for synthesis of ergosterol in the fungal wall. Fungi may become resistant to azole drugs by mutations resulting in altered 14α-demethylase production or affinity or mutations causing altered ergosterol content in the fungal membrane. Decreased permeability of the fungal membrane and efflux pumps that remove azole drugs from the cell are also potential mechanisms of resistance.

Flucytosine Resistance

Although most *Candida* species and *C. neoformans* are susceptible to flucytosine, about 10% of *Candida* isolates may be resistant prior to therapy. *C. lusitaniae* isolates

Table 3
Fungi with Frequent Resistance to Usual Therapies

Organism	Resistance
Candida albicans	Increasing emergence of resistance to azole drugs, especially to fluconazole in patients receiving long-term prophylaxis or treatment with fluconazole
Candida glabrata	Intrinsic decreased susceptibility to fluconazole, other azoles
Candida krusei	Intrinsic resistance to azoles drugs; may be selected in BMT patients on fluconazole prophylaxis
Candida lusitaniae	Usually resistance to amphotericin B and flucytosine
Candida tropicalis	Case reports of azole resistance
Aspergillus spp.	Resistant to fluconazole (itraconazole has activity)
Cryptococcus neoformans	Case reports of fluconazole resistance
Agents of zygomycosis	Resistant to azole drugs
Agents of hyalohyphomycosis	Some resistant to amphotericin B; most resistant to azole drugs
Paecilomyces lilacinus	Resistant to amphotericin B and flucytosine in vitro
Trichoderma spp.	Some resistant to fluconazole
Agents of phaeohyphomycosis	Increasing recognition of resistance to various antifungal agents
Scedosporium prolificans	Intrinsic resistance to all available drugs
Pseudallescheria boydii	Intrinsic resistance to amphotericin B
Trichosporon beigelii	Intrinsic resistance to amphotericin B
Saccharomyces cerevisiae	Resistant to fluconazole in vitro; may be resistant to other azoles.

are intrinsically resistant to flucytosine. In most cases, resistance to flucytosine usually emerges quickly when the drug is used as monotherapy. Therefore, when indicated, flucytosine should be used in combination with amphotericin B.

Amphotericin B Resistance

C. lusitaniae and *C. guilliermondii* are characterized by resistance to amphotericin B. *T. beigelii, P. boydii,* and some of the dematiacious fungi exhibit marked intrinsic resistance to amphotericin B. Development of secondary resistance to amphotericin B is still infrequently reported.

Amphotericin B exerts its predominant antifungal effect by binding to ergosterol in the fungal membrane and thus causing formation of pores in the fungal cell wall, leakage of intracellular contents, and cell death. Fungi can be resistant to amphotericin B if they have altered ergosterol content in the fungal membrane. Alternatively, resistance

can be due to altered β-1, 3-glycan composition in the fungal membrane, leading to decreased drug permeability.

Antifungal Susceptibility Testing

Traditionally, antifungal susceptibility testing was flawed by lack of standardization and inconsistency. In 1997, the National Committee for Clinical Laboratory Standards (NCCLS) approved standardized broth macrodilution and microdilution methods for the antifungal susceptibility testing of yeasts *(13).* The currently approved version (M27-A) can be used to determine susceptibility of *Candida* species and *C. neoformans* to amphotericin B, flucytosine, fluconazole, ketoconazole, and itraconazole. *Candida* species are classified as susceptible, susceptible-dose dependent, or resistant to fluconazole or itraconazole *(14,15).* Breakpoints have been established for *Candida* species for fluconazole (for all sites of infection) and for itraconazole (for mucosal sites only). For fluconazole, an MIC ≤ 8 mg/mL is considered susceptible, while ≥ 64 μg/mL implies resistance. MICs of 16–32 μg/mL are considered susceptible, depending on the dose of drug given. It is important to note that the standard breakpoints do not apply to *C. krusei,* which is considered intrinsically resistant to azoles. Breakpoints for amphotericin B are less clear, but MICs > 1 μg/mL may be associated with a poorer prognosis. Other methodologies such as E test strips are under investigation but are not yet reproducible or adequately standardized. Currently, no standardized antifungal susceptibility testing methods are available for any of the other fungi. However, a proposed standard for susceptibility testing for molds was recently published by the NCCLS, but the clinical significance remains unclear and breakpoints have not been determined *(16).* Currently, routine susceptibility testing of *Candida* spp. or *C. neoformans* is not recommended. However, when patients, especially immunocompromised patients, fail to respond to appropriate empiric therapy, susceptibility testing may be useful to guide therapy. In vitro susceptibility does not always predict successful therapy, as other factors such as underlying immune defects may be more important clinically. However, in vitro resistance usually predicts a high likelihood of therapeutic failure. At present, antifungal susceptibility testing should probably still be reserved for exceptional patient care situations and research purposes.

TYPES OF INFECTIONS

Candidiasis

Candida spp. can cause superficial (mucocutaneous) or deep infections *(17).* Candidal infections are extremely common, ranging from oral thrush to disseminated disease. Thrush most often occurs in patients on steroids or chronic antibiotics and in immunocompromised patients, especially those with HIV infection. In addition to the classic creamy white coating of the tongue and oral mucosa, oral candidiasis can present as an atrophic form, as angular cheilitis, or as *Candida* leukoplakia. In immunocompromised patients, *Candida* esophagitis can occur and usually presents with odynophagia. In HIV patients, painful swallowing can often be treated with an empiric course of antifungal therapy, reserving diagnostic workup for patients who fail.

Candida vaginitis is an extremely common condition; up to 70% of women will experience a "yeast infection" at some time in their lives (*see* Chapter 11, this volume). Severe and/or recurrent disease may signal underlying diabetes mellitus or HIV

infection, or be secondary to antibiotic use which alters the normal flora. Cutaneous candidiasis can present as *Candida* balantis, folliculitis, intertrigo, perianal involvement, or generalized skin eruptions. *Candida albicans* is frequently implicated as a cause of paronychia and onychomycosis. A condition termed chronic mucocutaneous candidiasis presents with persistent *Candida albicans* infections which are quite recalcitrant to treatment owing to the inability of the patients' T cells to respond to this yeast.

Candida spp. can also cause a wide range of invasive infections, usually in immunocompromised patients, including candidemia and deep infections of the eyes, liver, spleen, genitourinary tract, central nervous system (CNS) or other sites. *Candida* spp. are now the fourth most common isolate in nosocomial bloodstream infections, and blood cultures may be negative in an additional 50% of all cases *(18,19).*

Candida organisms are normal commensals colonizing the skin and gastrointestinal (GI) tract. Most cases of candidiasis reflect proliferation of these colonizers in the setting of immunosuppression or alteration of the other normal flora by antibiotic therapy or steroids. However, *Candida* infections can be transmitted from human to human, as evidenced by thush of the newborn. In addition, acquisition from exogenous sources is increasing, for example, nosocomially due to catheters, monitoring devices, or prosthetic implants.

Aspergillosis

Aspergillus species can cause superficial infections, involving skin or the upper respiratory tract. For example, *Aspergillus* sinusitis is a serious problem in bone marrow/stem cell recipients, patients with hematologic malignancies, and individuals with HIV infection. Invasive disease can occur in immunocompromised patients and is a harbinger of poor prognosis; correction of the underlying disease process is critical to survival. Involvement of the lung, CNS, GI tract, and multiple other organs can occur. Histopathologic evaluation will reveal fungal invasion of blood vessels with thrombosis and infarction of involved tissues.

As the number of patients immunocompromised by HIV, transplantation, and cytotoxic therapies has increased, the incidence of invasive aspergillosis has grown accordingly. Risk factors include quantitative or qualitative defects of neutrophils, steroid therapy, and diabetes. As many as 40% of patients with chronic granulomatous disease will suffer from *Aspergillus* infection, as well as ~10% of patients with transplants, HIV infection, or hematologic malignancies. *Aspergillus* spores are most commonly acquired via the respiratory tract and may manifest in several ways in the lungs, often reflecting host immune conditions. Allergic bronchopulmonary aspergillosis represents an allergic reaction to *Aspergillus* antigen, and occurs most often in individuals with asthma. Manifestations include eosinophilia and fleeting lung infiltrates. Aspergillosis can also present as a fungus ball or aspergilloma, often developing in patients with preexisting lung cavities due to tuberculosis or previous bacterial lung abscess. These patients may present asymptomatically when routine chest films are obtained or can have massive hemophysis. Invasive pulmonary aspergillosis occurs in immunocompromised patients and rarely in immunocompetent patients exposed to a heavy inoculum of *Aspergillus* spores. Prognosis is most dependent upon recovery from the underlying disease, usually correction of neutropenia.

Cryptococcosis

C. neoformans is ubiquitous in the environment and can cause disease in immunocompetent individuals as well as patients with abnormal cell-mediated immunity, especially those with HIV infection, bone marrow/stem cell transplants, or hematologic malignancies. The AIDS pandemic has been associated with a dramatic increase in cryptococcal infections. *C. neoformans* has a clear-cut prediction to cause CNS infections and cryptococcal meningitis is the most common invasive mycosis in AIDS, afflicting 5–10% of patients.

Cryptococcal infection usually presents as pneumonia or meningitis, but disseminated cases with multiorgan involvement can occur. Pulmonary cryptococcosis may be asymptomatic or cause frank pneumonia. The severity of cryptococcal pneumonia relates to the severity of underlying host immune defects, often remaining indolent in immunocompetent patients but potentially progressing rapidly in AIDS patients *(20).* Cryptococcal meningitis can present with a range of symptoms. Onset is often insidious with headache and somnolence, usually without obvious nuchal rigidity. Diagnosis depends upon the demonstration of the encapsulated yeast cells by India ink examination of cerebrospinal fluid and/or detection of capsular antigen. The severity and rapidity of the course of disease as well as the response to therapy appears to correlate with the immune status of the host.

Endemic Mycoses

These diseases (*see* Table 1) are endemic to specific geographic areas and cause widespread infection and disease. Blastomycosis and histoplasmosis are endemic to the Ohio River Valley states, coccidioidomycosis to the southwestern United States, while paracoccidioidomycosis is most frequent in Latin America and penicilliosis occurs in Southeast Asia and China. However, the mobility of patients around the globe necessitates the awareness that these diseases may have been acquired years earlier and manifest later during periods of immunosuppression after the individual has moved to a nonendemic area.

Blastomycosis is usually acquired by the respiratory route, and when symptomatic is manifested as pneumonia. Pulmonary involvement can be asymptomatic or cause nonspecific signs of fever, cough, and myalgias. Large inocula or underlying defects in immunity can result in severe pneumonia, including an adult respiratory distress syndrome (ARDS) picture. Later, patients can develop chronic pulmonary disease or can present with evidence of disseminated disease, especially skin or bone involvement. Complaints of bone or joint pain after a bout of blastomycosis should be investigated carefully with plain films and/or bone scan. Whether reactivation of blastomycosis due to immunosuppression occurs is controversial, but if it does it is clearly very unusual.

Coccidioidomycosis is increasing in incidence in the United States and has been classified as an emerging disease. The etiologic agent, *C. immitis,* is transmitted by inhalation of spores, especially in hot, dusty conditions. While many cases are asymptomatic, patients exposed to a heavy inoculum may develop nonspecific symptoms of fever, cough, and myalgias, with pneumonic infiltrates common. Individuals of African or Asian descent, Hispanics, Filipinos, pregnant women, and patients immunocompromised by HIV or other cell-mediated immune defects are at increased risk of severe, disseminated disease. Dissemination can result in involvement of bone, joints, skin, and visceral organs. CNS disease is a dreaded complication. Cutaneous hypersensitivity reactions including erythema nodosum or erythema multiforme are frequent.

Histoplasmosis is also acquired by the airborne route, often after exposure to bird or bat droppings. Patients who are spelunkers, who have worked in old barns or chicken coops, or who have been involved in renovating old homes are at particular risk. Histoplasmosis can cause a range of syndromes in the immunocompetent host, from asymptomatic infection to nonspecific flulike illness to frank pneumonia. In most cases, recovery will be complete, often without specific therapy. Infection can cause severe pneumonia if the inoculum is high and can progress to chronic pulmonary infection, particularly in patients with preexisting lung disease. Rarely, progressive fibrosis can develop, leading to mediastinal fibrosis and potentially compromising the esophagus, airways, or the superior vena cava and other blood vessels. Progressive, disseminated histoplasmosis can occur, especially in infants and immunocompromised adults. Patients with defective cell-mediated immunity, especially those with AIDS, are at particular risk. In addition, HIV-infected patients are at significant risk of developing reactivation of *Histoplasma* infection as immunosuppression progresses. Manifestations of disseminated disease include fever, pneumonia, sepsis syndrome, and visceral organ involvement.

Sporotrichosis is an endemic fungal infection that most often presents with cutaneous disease but extracutaneous syndromes can occur, especially in immunocompromised patients. Classically acquired by inoculation through the skin, infection most often presents with a lesion at the site of injury and lymphangitic spread of painless nodules. In unusual circumstances, the fungus disseminates hematogenously and causes bone, CNS, lung, or eye disease in the immunocompetent host or multifocal disease in immunocompromised individuals.

Zygomycosis

The zygomycetes, *Rhizopus* spp., *Absidia* spp., and *Mucor* spp., can cause subcutaneous or deep infections in immunocompromised patients. Neutropenic patients and those receiving steroid or cytotoxic therapy are at particular risk of disseminated disease. Infection may be rhinocerebral involving the sinuses and brain, pulmonary, or disseminated. The fungi invade blood vessels and cause thrombosis and infarction of tissue, resulting in black necrotic lesions and drainage. In patients immunocompromised by AIDS, disseminated infection can involve the lung, skin, and visceral organs. Pulmonary involvement is most characteristic of disease in renal transplant patients.

Hyalohyphomycosis

These mold infections occur almost exclusively in severely immunocompromised patients. Risk factors include cytotoxic chemotherapy, prolonged antibiotic therapy, organ transplantation, and HIV infection. Infection can present as noninvasive infection, especially of the skin, or as deep infection with pneumonia, sinusitis, or dissemination. *Fusarium* species may cause invasive sinus infections, skin involvement, pneumonia, or bloodstream infection and may disseminate to cause multifocal disease. *Paecilomyces* spp. have an interesting prediliction for ocular involvement and can manifest as keratitis and endophthalmitis. In other patients, disseminated disease with pneumonia, sinusitis, and fungemia may occur.

Phaeohyphomycosis

The dematiacecus fungi can cause a variety of diseases in immunocompromised patients. Initially, disease may manifest as skin, sinus, lung, or CNS involvement, but

can progress to disseminated disease with involvement of multiple sites. Disease mimics that of other invasive fungal infections, but the diagnosis can be made with special stains of tissue samples to demonstrate the melanin characteristic of these organisms.

Other Serious Fungal Diseases

P. carinii has recently been reclassified as a fungus but clinical management of infections caused by this organism differs significantly from that of other fungi. *P. carinii* can be found in the lungs of many normal humans, but can cause severe pulmonary and extrapulmonary disease in immunocompromised individuals. Long recognized as a pathogen in malnourished or very premature babies and in patients with marked defects in cell-mediated immunity due to cytotoxic therapy, *P. carinii* has risen to prominence in the era of AIDS. *P. carinii* pneumonia (PCP) occurring in homosexual men was one of the first signals of the HIV pandemic and was the most important opportunistic infection early in the epidemic. Although interventions for prophylaxis and treatment of PCP are now widely available, it remains an important cause of morbidity and mortality in this population. *Pneumocystis* most often manifests as pneumonia. Although interstitial infiltrates are classic, it is important to remember that a wide variety of chest film findings can be present, including normal films. PCP should be included in the differential diagnosis of AIDS patients with shortness of breath and hypoxia, regardless of the X-ray findings. Extrapulmonary involvement with *Pneumocystis* may manifest in the lymph nodes, spleen, liver, bone marrow, GI tract, eyes, or thyroid. AIDS patients receiving PCP prophylaxis with aerosolized pentamidine are at particular risk of extrapulmonary involvement, as the drug protects only locally in the lung. As a result other systemic approaches to PCP prophylaxis are now preferred by many.

P. boydii has emerged as an important cause of disease in severely immunocompromised patients. Infection manifests most commonly as pneumonia, but sinusitis, skin infection, CNS or eye involvement, or disseminated disease can occur. Because this species is often resistant to amphotericin, prognosis is poor unless the underlying disease process can be corrected.

Other emerging infections are being recognized in severely immunocompromised patients. *M. furfur* is a lipophilic fungus that causes dermatophytosis in the normal host. However, as a result of its lipophilic nature, it can grow in lipid-rich solutions, including parenteral hyperalimentation supplemented with fatty acids. Immunocompromised, especially neutropenic patients receiving such therapy, may develop *Malassezia* infection, manifested by follicular skin lesions or disseminated disease in the lungs and other organs. *T. beigelii* has also emerged as a feared fungal infection in neutropenic patients. Skin, lung, or sinus involvement can progress to disseminated disease with multifocal infection. Reversal of the neutropenia is critical to survival. *Saccharomyces cerevisiae* or Brewer's yeast has been recognized as a cause of vaginitis and can also rarely cause disseminated infection.

Chromomycosis

This chronic fungal infection occurs throughout the world, especially in tropical regions and manifests as verrucous lesions at a site of inoculation of the organism, usually on an extremity. Infection remains localized within the cutaneous and subcutaneous tissues but can cause disfiguring lesions that may interfere with function. Over

time, the lesions can enlarge and become clumped together. Lesions can be pruritic but are rarely painful. Medical attention is usually sought because of bacterial superinfection, lymphedema, bulky lesions, or for cosmetic reasons. Invasion of bone does not occur, in contrast to mycetoma.

Mycetoma

Also known as Madura foot, mycetoma is a chronic, slowly progressive fungal infection of skin, fascia, muscle, and bone. Infection is generally acquired via accidental inoculation, usually into an extremity. The localized swelling and granuloma formation can progress to produce a disfigured, swollen foot with multiple sinuses, usually over the course of years. Medical care is usually sought because of secondary bacterial infection or for cosmetic requests. Because mycetoma can also be caused by actinomycetes, it is important to establish whether the etiology is fungal.

Dermatophytes

These mold infections are extremely common causes of superficial fungal lesions of the skin throughout the world *(21).* The annual cost in the United States exceeds $400 million. Dermatophytoses can be acquired from other people, animals, or the environment. Although they do not generally cause life-threatening illness, they do affect quality of life and social embarassment is a concern. Lesions may appear as annular patches with raised margins and inflammation. Clinical appearances varies with the site and host immune response, as well as with the causative fungal species. Tinea pedis is most often caused by *T. rubrum* and *T. mentagrophytes* and results in the well-known lesions of "athlete's foot." Tinea cruris may be caused by *T. rubrum* and *E. flaccosum* and manifests groin lesions. Tinea corporis or ringworm may be caused by several dermatophytes, and clinical patterns vary with the site of infection and causative organism. Scalp ringworm or tinea capitis is a disease of children and is widespread in the United States. Scaling of the scalp skin is associated with erythema and alopecia. Onychomycosis usually occurs in patients with adjacent dermatophyte infection of the toes or fingers, and should be distinguished from onychomycosis due to *Candida* spp. The dermatophyte infections may be associated with "id reactions," leading to additional rash, which have been attributed to delayed-type hypersensitivity reactions to intradermal trichophyton.

TREATMENT

Antifungal Drugs

Antifungal agents are much more limited in number than are antibacterial drugs *(22–24).* Unfortunately, many of the available agents have significant cost and toxicity. Currently available drugs for the treatment of fungal infections are amphotericin B and the newer liposomal forms of amphotericin, flucytosine, and the azole drugs *(25,26).*

The polyene amphotericin B is the mainstay of therapy for serious fungal infections and remains the most broad-spectrum antifungal agent available. Its broad spectrum of activity and clinician experience with its use make it the drug of choice for *Aspergillus* infections and most other deep mycoses, despite its associated nephrotoxicity and other side effects. New liposomal amphotericin products are available that have less nephrotoxicity than the deoxycholate form *(27,28).* While effective in treating many serious

fungal infections, their high cost has prompted many organizations to limit their use. Indeed, the cost–benefit comparison of amphotericin B vs. the new liposomal preparations has been the subject of much debate. Many institutions have restricted the use of liposomal preparations to patients who have developed nephrotoxicity in response to amphotericin B.

The new azole drugs represent an exciting advance for the treatment of serious fungal diseases *(29,30).* For the first time, oral agents with reliable efficacy are now available for the treatment of several of the fungal diseases. Fluconazole is a relatively nontoxic drug that has good efficacy in the treatment of *Candida* and some other fungal infections. It is available in both an oral and an intravenous form. Itraconazole has a broader spectrum of activity, including activity against some *Aspergillus* organisms, as well as *Candida, Blastomyces,* and *Histoplasma.* New azole drugs such as voriconazole appear promising. Azoles have effects on the P450 system, and other medications should always be reviewed to prevent adverse drug interactions.

Flucytosine is less widely used than amphotericin B or the azoles, owing to its more limited spectrum of activity and potential toxicity. However, flucytosine can play an important role in treatment of cryptococcal meningitis when used in combination with amphotericin B. To prevent toxicity, especially bone marrow suppression, serum drug levels must be monitored. Suggested therapeutic choices for the major fungal infections are outlined in Table 4, based on recent practice guidelines suggested by the Infectious Disease Society of America (IOSA) *(31).*

Treatment of Specific Fungal Infections

Candidiasis

Guidelines for the treatment of mucocutaneous candidiasis have been published by the American Academy of Dermatology *(21).* Thrush due to *Candida* spp. can be treated with many different agents, including clotrimazole troches, nystatin swish and swallow, amphotericin suspension, or the oral azoles. The widespread use of fluconazole for treatment and prevention of thrush in patients with HIV has led to the emergence of azole-resistant strains *(32).* For this reason, many experts now urge use of nonazole drugs as a first choice, with fluconazole reserved for cases in which other drugs such as nystatin have failed. However, the efficacy and ease of use of fluconazole have interfered with widespread acceptance of this approach.

Many agents are available for the treatment of *Candida* vaginitis. A single dose of fluconazole is often effective. Because concerns about resistance are much lower in the situation in which short-term therapy is needed, this practice has been widely adopted. However, in some patient populations in which fluconazole prophylaxis has been used, especially HIV patients, vaginitis resistant to azoles has been recognized.

The management of serious *Candida* infections has given rise to much debate. A consensus publication on an approach to management and prevention of severe *Candida* infections has been published *(33).* Practice guidelines for treatment of candidiasis have recently been issued by the IOSA *(34).* The need for a more aggressive approach to management of *Candida* infections was advocated, including emphasis of the need to treat all patients with candidemia. In most cases, fluconazole was considered appropriate first-line therapy for stable patients, while amphotericin B should still be used for those with life-threatening disease.

Table 4
Approach to Treatment of Fungal Infections

Disease	Treatment Options
Classic Infections	
Aspergillosis	
Allergic bronchopulmonary aspergillosis	None or—itraconazole
Aspergilloma	Observation; surgery; itraconazole
Invasive	Amphotericin B or liposomal amphotericin, then consider itraconazole
Candidiasis	
Mucocutaneous	Thrush-clotrimazole troches, nystatin swish and swallow, fluconazole, amphotericin solution, itraconazole if refractory; esophagitis—fluconazole, amphotericin if severe; vaginitis—fluconazole; topical preparations such as nystatin, miconazole
Invasive	Amphotericin B; fluconazole effective for most *C. albicans*
Cryptococcosis	
Nonmeningeal	Fluconazole
Meningitis	Amphotericin B + flucytosine followed by fluconazole
Sporotrichosis	Potassium iodide if limited; itraconazole; amphotericin B
Endemic infections	
Histoplasmosis	Observation if not severe; itraconazole; amphotericin B if severe
Blastomycosis	Itraconazole; amphotericin B if severe
Coccidioidomycosis	
Nonmeningeal	Observation if acute, not severe; fluconazole or itraconazole; amphotericin B if severe
Meningitis	Amphotericin B or fluconazole
Paracoccidioidomycosis	Itraconazole; amphotericin B if severe
Penicilliosis	Amphotericin B; itraconazole

Other invasive infections	
Zygomycosis	Correct predisposing disease process plus amphotericin B or liposomal amphotericin plus surgical debridement if possible (azoles not effective)
Hyalohyphomycosis	Correct predisposing disease process including growth factors for neutropenia, plus amphotericin B or liposomal amphotericin, itraconazole (for some species)
Phaeohyphomycosis	
Keratitis	Topical antifungal drugs
Skin	Surgical debridement plus itraconazole ± flucytosine
Other	Amphotericin B plus itraconazole ± flucytosine; plus surgical debridement if possible
Miscellaneous	
Invasive	
Pneumocystis carinii	Trimethoprim–sulfamethoxyzole; intravenous pentamidine; others
Pseudallescheria boydii	Surgical drainage if possible; Optimal treatment unknown—? azole drugs (often resistant to amphotericin B)
Malassezia furfur	Fluconazole; remove catheter
Trichosporon beigelii	Correct predisposing disease process including growth factors for neutropenia plus fluconazole.
Saccharomyces cerevisiae	Amphotericin B ± flucytosine (azoles usually not effective)
Chromomycosis	Surgical excision if possible; optimal treatment unknown—trial of itraconazole often warranted
Mycetoma	Itraconazole effective in some cases. Surgical debulking if possible (R/O disease due to actinomycetes)
Dermatophytes	
Onychomycosis	Terbinafine or itraconazole (intermittent therapy)
Tinea skin infection	Topical azole drugs or terbinafine if localized; oral terbinafine or itraconazole

Uncomplicated candidemia can usually be treated successfully with fluconazole for 21 d *(33)*. Complicated cases, such as those in immunocompromised patients or involving resistant organisms, require use of amphotericin B or longer courses of fluconazole. Given the difficulty with treating established fungal infections, prevention should be emphasized. The benefit of fluconazole prophylaxis in patients undergoing bone marrow/stem cell transplantation is widely accepted *(36)*. Studies are underway to determine the benefit of azole or amphotericin prophylaxis in other high-risk populations, such as solid organ recipients, patients with hemotologic malignancies receiving cytotoxic therapy, and patients in surgical ICUs. However, the emergence of resistant fungal infections in patients prescribed fluconazole prophylaxis makes this an area of ongoing controversy *(37)*.

The timing of initiation of empiric therapy for candidiasis in high-risk patients is also a subject of debate. Neutropenic patients with fever who fail to respond after 5–7 d of empiric antibacterial therapy may benefit from empiric treatment with antifungal agents. Furthermore, the high risk of candidemia in surgical ICU patients, and the high rate of failure to isolate the organisms from blood cultures in that setting, has led many clinicians to use empiric antifungal therapy in this population as well; further study is needed to define the optimal approach.

Aspergillosis

The IOSA has issued practice guidelines for the treatment of aspergillosis *(38)*. Invasive infections due to *Aspergillus* spp. should usually be treated with amphotericin B. Recovery from disseminated disease is most often dependent on correcting the underlying immune defect, especially neutropenia. The use of liposomal amphotericin B should be considered in patients unable to tolerate amphotericin B deoxycholate, especially those with nephrotoxicity. Treatment of aspergillosis most often requires use of high daily doses (0.8–1 mg/kg) and significant total doses (1.5–2 g). Itraconazole has efficacy against *Aspergillus* and consideration can be given to switching to the azole drug once the infection has been controlled. Decisions on when to switch from amphotericin B to itraconazole and duration of therapy must be tailored to the individual, keeping in mind the status of the underlying disease. Combination therapy with amphotericin B and flucytosine has been advocated by some experts, especially if infection occurs at sites not well penetrated by amphotericin B, such as the CNS. Rifampin may provide some synergistic benefit as well. Surgical therapy can be considered as an adjunct for patients with isolated foci of disease.

Much controversy has been raised about the use of combined amphotericin B and itraconazole. Potential antagonism has been postulated, possibly mediated by azole-induced alterations in ergosterol content of the fungi, making them less susceptible to amphotericin. However, there is little documentation of clinically significant detrimental interactions and many clinicians use amphotericin B and itraconazole together for life-threatening infections. Further study is needed.

Cryptococcosis

The IOSA has issued practice guidelines for the treatment of cryptococcosis *(39)*. Amphotericin B with or without flucytosine remains the drug of choice for serious cryptococcal disease. Renal function and blood counts must be monitored closely with these potentially toxic drugs. Prolonged therapy may be necessary to prevent relapse.

Fluconazole also has efficacy, and may be considered in less severely ill patients. In AIDS and probably other immunosuppressed patients, cryptococcal meningitis is never cured, just controlled. Therefore, in HIV-infected individuals, lifelong maintenance therapy with fluconazole is indicated. All patients should be followed closely for signs of relapse, which can occur in the CNS or in sequestered foci such as the prostate.

Endemic Mycoses

The IOSA has issued practice guidelines for the treatment of blastomycosis *(40)*, histoplasmosis *(41),* coccidoidomycosis *(42),* and sporotrichosis *(43).*

The introduction of itraconazole has significantly simplified the management of blastomycosis. While amphotericin B remains the drug of choice for treatment of severe disease, itraconazole is effective in treating less serious illness. Monitoring after completion of therapy for evidence of skin or bone involvement is necessary. Prolonged treatment courses may be needed for treatment of chronic pulmonary disease or disseminated disease.

Histoplasmosis also responds to either amphotericin B or itraconazole, with the former required for severe disease, especially if it occurs in immunocompromised patients. Itraconazole can be used for most disease in immunocompetent hosts and in nonsevere disease in immunocompromised patients. Because of the frequency of reactivation, especially in AIDS patients, HIV-infected individuals should receive lifelong maintenance therapy with itraconazole.

Disseminated coccidioidomycosis should be treated with amphotericin B in cases of severe disease in immunocompromised or other high-risk individuals. Both fluconazole and itraconazole have activity against *Coccidioides immitis* and can be used for treatment of mild disease in immunocompetent individuals and for prolonged therapy after response to amphotericin B.

Localized sporotrichosis may respond to potassium iodide but the azole drugs, particularly itraconazole, are more reliable. Amphotericin B should be used for treatment of disseminated disease. Amphotericin B is the drug of choice for treatment of disseminated penicilliosis in AIDS patients, although itraconazole may also be effective.

Zygomycosis

Azoles are not effective and amphotericin B is the drug of choice for treatment of zygomycete infections. However, antifungal therapy will be effective only if correction of the predisposing disease process can be accomplished. The need for high doses of amphotericin B has led to interest in the use of liposomal preparations, but studies are limited, and concerns have been raised about CNS penetration. Surgical debridement should be undertaken if possible. Mucormycosis with rhinocerebral involvement in diabetics should be treated by correction of the diabetic ketoacidosis, amphotericin B, and surgery.

Hyalohyphomycosis

Successful treatment of these infections is usually dependent on correction of the predisposing immune deficits. The use of growth factors to urgently reverse neutropenia has been advocated. For fusariosis, amphotericin B or liposomal amphotericin with or without flucytosine have been used most often, and a role for itraconazole is being investigated. Although some *Paecilomyces* species are susceptible to amphotericin B, other species are not. Use of experimental drugs such as voriconazole should be considered.

Phaeohyphomycosis

When agents of phaeohyphomycosis cause isolated ocular involvement, topical antifungal agents may be effective. Optimal treatment regimens for disseminated disease have not been established and response to amphotericin B or azole drugs is variable. Surgical debridement should be considered whenever possible.

Pneumocystis carinii

The treatment of *P. carinii* pneumonia is quite distinct from that of most fungal infections. Trimethroprim–sulfamethoxyzole is the drug of choice for both prophylaxis and treatment. Unfortunately, a significant proportion of AIDS patients have allergies to sulfa agents and require the use of alternative agents. Dapsone, atovaquone, and aerosolized pentamidine are effective prophylactic drugs and intravenous pentamidine and atovaquone can be used for treatment. In AIDS patients, prophylaxis should be instituted for all patients with CD4 counts < 200 cells/mm^3 and patients with previous PCP episodes. It is possible that prophylaxis can be discontinued in AIDS patients whose CD4 counts increase significantly to > 200 cells/mm^3 after institution of highly active antiretroviral therapy, but further study of such immune reconstitution is needed before definite recommendations can be made.

Other Invasive Mycoses

Disseminated infection with *M. furfur* should be treated with fluconazole. Removal of the catheter used to administer the fatty acid containing hyperalimentation solution is critical. *T. beigelii* infections can be very difficult to treat and reversal of neutropenia with growth factors should be considered. Aggressive therapy with fluconazole and possibly amphotericin B is necessary. Invasive *Saccharomyces* infection should be treated with amphotericin B, with or without flucytosine. Symptomatic vulvovaginitis may also require therapy with amphotericin, as azoles are usually ineffective.

Chromomycosis

These infections are usually not life threatening, and the goal of therapy is often cosmetic improvement. Surgical excision for debulking or cryotherapy for small lesions may be helpful. Optimal treatment is incompletely defined, but consideration can be given to a trial of itraconazole.

Mycetoma

Because these infections can progress to bony destruction, improved therapy is desirable. Surgical excision may be helpful for debulking but amputation should be avoided. It is critical to ensure that disease is truly of fungal origin and is not due to actinomycetes which should be more amenable to antimicrobial therapy. A trial of itraconazole is reasonable.

Dermatophytes

The American Academy of Dermatology has published guidelines to assist the clinician in management of superficial mycotic infections of the skin. The guidelines cover six areas related to superficial mycoses: (1) mucocutaneous candidiasis; (2) tinea capitis and tinea barbae; (3) onychomycosis; (4) pityriasis versicolor; (5) piedra; and (6) tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis *(21).* Pityriasis (tinea) versicolor often responds to therapy with topical imidazoles or other antifungals, but

severe disease may require therapy with oral azole drugs. In contrast, tinea capitis and tinea barbae usually require management with oral azoles, with topical agents relegated to an adjunctive role only. The addition of corticosteroids or antibacterial drugs may be necessary. Family members should be evaluated. Tinea corporis, cruris, faciei, manuum, and pedis will respond to topical antifungal agents if the condition is noninflammatory and mild. Oral azole drugs should be used if lesions are inflammatory.

Onychomycosis can be a challenging clinical problem, but new drugs offer improved options. Itraconazole has good efficacy in treatment of onychomycosis but traditional prolonged treatment courses can be quite expensive. Terbinafine is a more cost-effective agent and is now recommended as the first-line agent by many experts. The recent recognition of the efficacy of intermittent therapy with either drug can further reduce cost. Aggressive management is particularly important in immunocompromised patients, including those with HIV infection or diabetes.

Special Considerations for Treatment of Resistant Fungi

Because *C. krusei* is inherently resistant to fluconazole, treatment with amphotericin B is mandatory. *C. glabrata* also demonstrates reduced susceptibility to azoles and amphotericin B may be necessary. Isolates resistant to azoles, especially fluconazole, are rising for *C. albicans,* and case reports of resistance in non-*albicans Candida* spp. are increasing in frequency. When patients fail to respond to azole therapy, the possibility of resistant organisms should be considered, and switching to amphotericin B may be appropriate. Although not widely routinely available, *Candida* susceptibility testing is an option and standards have been established by the NCCLS *(13,15,26).* Testing may be indicated for patients who fail to respond to appropriate empiric therapy. Finally, *C. lusitaniae* is remarkably resistant to amphotericin B and flucytosine, but usually remains susceptible to fluconazole.

If patients with candidiasis fail to respond to therapy with fluconazole, alternative agents should be considered. Increasing the dose of fluconazole may be effective in treating some infections caused by *C. albicans* and non-*albicans Candida* spp. (e.g., *C. glabrata*) with relative resistance to fluconazole. Dosages as high as 800 mg/d have been used in recalcitrant cases. For fungi without cross-resistance to other azoles, itraconazole may be effective. Oral amphotericin can be used for oropharyyngeal candidiasis in HIV patients with disease unresponsive to azoles. Intravenous amphotericin B may be necessary in severe cases. New experimental drugs such as voriconazole offer hope for the future.

Aspergillus species will not respond to fluconazole, and amphotericin B should be used for treatment of serious disease. Itraconazole does have efficacy and can be used for less severe disease or for completion of therapy after initial response to amphotericin B.

Case reports of fluconazole resistance to *C. neoformans* have been reported, although the drug has good efficacy in most cases. Amphotericin B and flucytosine remain the mainstay of initial therapy, although fluconazole is occasionally used for the entire treatment course in some patients and is an important drug for maintenance therapy. If patients fail on fluconazole, a switch to amphotericin B is appropriate. Consideration can be given to susceptibility testing of *Cryptococcus* organisms in cases of nonresponse to the azole drugs.

Table 5
Potential New Antifungal Drugs

- Echinocandins (1, 3-β-D-glucan synthase inhibitors)
- New azole drugs
  - Voriconazole
  - SCH56592 (derivative of itraconazole)
- Chitin synthase inhibitors
- Sodarins (protein synthesis inhibitors)
  - Nikkomycin
- Dicationic aromatic compounds

The zygomycetes and many of the agents of hyalohyphomycosis and phaeohyphomycosis are generally resistant to the azole drugs. In addition, some fungi causing hyalohyphomycosis are resistant to amphotericin B. For example, *Paecilomyces lilacinas* is resistant to amphotericin B and flucytosine in vitro. Azole drugs should be used. *Sedosporium prolificans,* which causes disease in the category of phaeohyphomycosis, demonstrates intrinsic resistance to all currently available antifungal drugs. *P. boydii* and *T. beigelii* also are resistant to amphotericin B. Azoles can be used but treatment is difficult and prognosis poor unless the underlying immune defects can be reversed. New, investigational drugs are under study and are urgently needed for management of these challenging diseases.

New Antifungal Drugs

The increase in fungal infections caused by well-recognized pathogens, the expanded recognition of resistant fungal strains, and the emergence of infections due to strains previously considered nonpathogenic highlight the need for development of innovative approaches to antifungal therapy. Several new drugs are under investigation and initial results portend an exciting future *(1,22,23,29)* (Table 5).

A number of new azole drugs are currently being studied. Voriconazole is a new triazole derivative of fluconazole currently in phase III trials that has a broad spectrum of activity against *Candida* spp., *Aspergillus* spp., dimorphic fungi, and other molds *(29).* Voriconazole seems to have activity against *Candida* spp. such as *C. krusei* which are resistant to fluconazole. Voriconazole also appears to have better activity against *Aspergillus* spp. than itraconazole. SCH 56592 is a derivative of itraconazole. This new drug appears to have better activity against *Aspergillus* spp. than itraconazole and broad-spectrum activity against a variety of yeasts, dimorphic fungi, and molds, including the zygomycetes and dematiaceous fungi. Other azole drugs are in earlier stages of development.

An exciting new class of antifungal function is the echinocandins. These drugs are fungicidal due to their inhibition of 1, 3β-D glucan synthase and consequent inhibition of β-glucan synthesis in the fungal cell wall. These compounds appear to have activity against *Candida* spp., *Aspergillus* spp., fungi causing endemic mycoses, and *P. carinii,* as well as other yeasts and molds. Nikkomycin is a fungicidal compound that inhibits chitin synthesis in the fungal cell wall. It may particularly prove useful in treatment of infections due to the endemic fungi, especially coccidioidomycosis. Studies are needed to determine if fungal cell membrane active agents (azoles and polyenes) and

cell wall active agents (nikkomycin and echinocandins) might be synergistic if used in combination.

Other Approaches

Other approaches to optimizing antifungal therapy include use of growth factors to correct underlying neutropenia and cytokines and other immunomodulatory interventions. Further studies to determine which patient populations will benefit from antifungal prophylaxis are also needed *(44–46)*.

Key Points

- While most *Candida albicans* remain sensitive to fluconazole and amphotericin B, fluconazole-resistant *C. albicans* and non-*albicans Candida* spp. that may be less susceptible to azoles are being recognized with increased frequency.
- *C. krusei* is resistant and *C. glabrata* demonstrates decreased susceptibility to fluconazole. *C. lusitaniae* is resistant to amphotericin B and flucytosine, but remains susceptible to azoles.
- *Aspergillus* spp. do not respond to fluconazole, but amphotericin B and itraconazole may have efficacy, especially if predisposing immune defects can be corrected.
- Itraconazole now plays an important role in management of blastomycosis and histoplasmosis, although amphotericin B is still used for severe disease.
- Treatment of zygomycosis, hyalohyphomycosis, and phaeohyphomycosis is challenging and involves aggressive antifungal therapy, adjunctive surgery if possible, and correction of underlying immune defects.
- Guidelines for management of dermatomycoses have been published by the American Academy of Dermatology.
- Susceptibility testing for *Candida* species and *Cryptococcus neoformans* has now been standardized but is still used predominantly for exceptional patient care decisions and research purposes.
- New antifungal drugs are urgently needed and several are currently being studied.
- Practice guidelines are available from the IOSA to guide treatment of many fungal diseases *(31)*.

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III
Management of Infectious Diseases

7
Upper Respiratory Infections and Acute Bronchitis

Arch G. Mainous III and William J. Hueston

INTRODUCTION

Upper respiratory infections include uncomplicated upper respiratory infections also known as the "common cold," acute otitis media, pharyngitis/tonsillitis, and acute sinusitis. These conditions, along with acute bronchitis, are very common illnesses that are seen often in outpatient settings and are widely treated with antibiotics; in fact, they are the primary indications for outpatient antibiotic prescriptions. These conditions tend to have overlapping clinical characteristics, yet evidence regarding the utility of antimicrobial treatments varies across different infections.

UNCOMPLICATED UPPER RESPIRATORY INFECTION/COMMON COLD

Clinical Description

Uncomplicated upper respiratory infections (URIs) are characterized by rhinorrhea, nasal congestion, sneezing, sore or "scratchy" throat, and cough *(1)*. The incubation period varies between 48 and 72 h. In some cases a low-grade fever is present, but temperature elevation in adults is rare. The early symptoms may be minimal and limited to malaise and nasal symptoms. The nasal discharge is initially clear and watery. There is a subsequent transition period where the nasal discharge becomes viscous, opaque, and discolored (white, yellow, green) *(2)*. The color of the secretions is not predictive of a bacterial infection. The clinical presentation is similar in both adults and children. The episode tends to be self-limited. The median duration of a cold is 1 wk, with most patients improving by the 10th day, but lingering symptoms may last up to 2 wk.

Epidemiology

URIs, or the "common cold," are exactly as the name implies—common. URIs are consistently one of the five most common diagnoses in ambulatory physician office visits *(3–5)*. Adults have two to four URIs annually and children in day care have as many as six or seven *(6,7)*. Although URIs are mild, self-limited, and of short duration, they are a leading cause of acute morbidity and of industrial and school absenteeism *(8)*. Each year, URIs account for 170 million d of restricted activity, 23 million d of school absence, and 18 million d of work absence.

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The significant costs of URIs can be conceptualized as both direct and indirect. The direct costs of URIs include those associated with the substantial number of office visits. In addition, microbiologic and laboratory diagnostic tests are sometimes performed but are of dubious clinical value and therefore contribute unnecessarily to the cost of URIs *(9).* The direct costs for URIs also include treatment. Americans spend between $1 and $2 billion annually on the more than 800 over-the-counter cough and cold preparations available *(10,11).*

Indirect costs for URIs include productivity losses related to lost workdays for adults who are sick as well as adults who need to care for sick children. Other indirect costs that are many times overlooked are the impact of URIs on missed opportunities to immunize young children. Although the interpretation of guidelines by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices, particularly for fever and moderate illness, rests with the clinician *(12,13),* a large proportion of children are not immunized on schedule because of visits for URIs *(14).* This finding also suggests additional visits for immunizations, thereby requiring additional direct costs and indirect costs inherent in taking children to the physician's office.

The mechanisms of transmission suggest that URIs can be spread through contact with inanimate surfaces *(15)* and hand-to-hand contact *(16).* URIs have a seasonal variation, with an increased prevalence in the United States between September and March. It is unclear why this variation exists although it may be related to increased crowding of indoor populations in the colder months. Temperature is not the key to seasonal variation without the presence of a pathogen. Evidence from Antarctica showed that spacious well-ventilated rooms reduced transmission of URIs compared to crowded poorly ventilated rooms regardless of temperature *(17).*

Etiology

Viruses have been shown to be the major pathogens in URIs *(18).* A recent study established viral etiology in 69% of URIs *(19).* Rhinoviruses were found in 52% of the patients by viral culture or polymerase chain reaction (PCR) assay. Coronaviruses were the second most common group of causative agents, followed by influenza A or B virus. Identified bacterial pathogens were *Chlamydia pneumoniae, Haemophilus influenzae, Streptococcus pneumoniae,* and *Mycoplasma pneumoniae.* None of the patients had β-hemolytic Group A *Streptococcus.* In terms of bacterial pathogens, infections without evidence of a viral infection occurred in only 0.05% of the cases.

Treatment

Antibiotics are widely prescribed for URIs *(20,21).* A recent study in a Medicaid population showed that 60% of cases of acute nasopharyngitis (e.g., common cold) were treated with antibiotics *(20).* Unfortunately, controlled trials of antimicrobial treatment of URIs have consistently demonstrated no benefit *(22–27).* In eight trials of antimicrobial treatment of URIs six found no difference between the groups either in terms of improvement or complications. Complications tend to be minimal and occur at a rate of 10–15%. One trial found some slight benefit in decreasing the presence of purulent rhinitis *(28).* Another found a decrease in rhinorrhea at d 5 but no difference between the groups at d 10 *(29).* Similarly, an additional trial attempted to isolate "bacterial colds" for which antibiotics might be effective treatments *(30).* Although there

was some indication of patient improvement at d 5, the differences were no longer apparent by d 10. It is important to remember that the normal presentation of a URI is 1 wk to 10 d.

Although recent research focusing on ipratropium bromide and zinc gluconate has shown some promise, few successful treatments have been identified for URIs *(10,31,32).* Antihistamines, with a few exceptions, have not been shown to be effective treatments *(10,33,34).* The most effective symptomatic treatments are over-the-counter decongestants *(10).*

ACUTE SINUSITIS

Clinical Description

Acute sinusitis has considerable overlap in its constellation of signs and symptoms with URIs. One half to two thirds of patients with sinus symptoms seen in primary care are unlikely to have sinusitis *(35).* In 300 patients who presented with a URI, 19% had radiographic evidence of maxillary sinusitis, but had no symptoms of sinus infection *(30).* URIs are often precursors of sinusitis and at some point symptoms from each condition may overlap. Sinus inflammation from a URI without bacterial infection is also common. In a series of 60 children undergoing computerized tomography (CT) for non-sinus-related diagnoses, 47% had evidence of sinus inflammation with no clinical signs of sinusitis and with complete resolution following their viral illness *(36).*

Acute sinusitis tends to start with a URI that leads to sinus ostial obstruction. The signs and symptoms that increase the likelihood that the patient has acute sinusitis are a "double sickening" phenomenon whereby the patient seems to improve following the URI and then deteriorates, maxillary toothache, purulent nasal discharge, poor response to decongestants, and a history of discolored nasal discharge *(37,38).* Other authors have stressed that the symptoms need to persist longer than 1 wk to distinguish sinusitis from a URI *(39).* It should be pointed out that the commonly used sign of facial pain or swelling has low sensitivity for acute sinusitis *(38).*

Epidemiology

Because sinusitis is most often a complication of upper respiratory viral infections, it follows the same seasonal pattern as colds. This produces a winter peak with more cases seen in those exposed to upper respiratory tract infections.

In children seen in a large health system, sinusitis is frequently found as a co-morbidity with otitis media. Nearly half of all children with sinusitis also had otitis media *(40).* Children are also more likely to have posterior ethmoidal and sphenoid inflammation while adults have mainly maxillary and anterior ethmoidal sinusitis *(41).* Some medical conditions may increase the risk for sinusitis. These include cystic fibrosis, asthma, immunosuppression, and allergic rhinitis *(42).* Cigarette smoking may also increase the risk of bacterial sinusitis during a cold because of reduced mucociliary clearance.

Etiology

Sinus inflammation can be caused by viral, fungal, and bacterial infections as well as allergies. The majority of acute sinusitis is caused by viral infection. As indicated

previously, many cases of the common cold have concomitant sinus inflammation. The inflammation associated with viral infections clears without additional therapy.

Bacterial superinfection of URIs is rare and occurs in only 0.5–1% of colds. Studies examining the treatment of sinusitis confirm that response rates to antibiotics are either small *(43)*. When sinusitis is confirmed by CT scan, response rates to antibiotics are improved *(44)*.

Cultures of material obtained from patients with sinusitis show that the most prevalent organisms are *Streptococcus pneumoniae* and, especially in smokers, *H. influenzae*. These two organisms are present in 70% of cases of bacterial acute sinusitis *(45)*. When antibiotics are used for the treatment of bacterial sinusitis, selection of antibiotics should include sufficient coverage of these two organisms.

Fungal sinusitis are very rare and usually occur in immunosuppressed individuals or those with diabetes mellitus *(45)*.

Treatment

Antibiotics are commonly prescribed for adult patients who present with complaints consistent with acute sinusitis. The effectiveness of antibiotics is unclear. Three recent placebo-controlled, double-blind, randomized trials in general practice settings have yielded mixed results *(43,44,46)*. Two of these trials showed no beneficial effect of antibiotics *(43,46)* while the third demonstrated a significant effect of penicillin and amoxycillin *(44)*. The trial showing an effect used more stringent enrollment criteria than the other two, which are more consistent with those used in daily practice by primary care physicians. These data suggest that patients with more severe signs and symptoms may benefit from an antibiotic. If an antibiotic is to be used, some evidence with trimethoprim–sulfamethoxazole suggests that treatment of short duration (e.g., 3 d) is as effective as longer treatment *(47)*. Further, narrow-spectrum agents seem as effective as broad-spectrum agents *(48)*.

Antibiotics have some utility in treating acute sinusitis in patients with severe signs and symptoms. If antibiotics are to be used, short-course therapy with narrow-spectrum agents is recommended. The key to judicious use of antibiotics is to first make an accurate diagnosis of sinusitis rather than overtreating URIs.

ACUTE OTITIS MEDIA

Clinical Description

Acute otitis media is one of the most common pediatric conditions seen in primary care. In 1990 there were 12.8 million episodes of acute otitis media in children <5 yr old in the United States, with total estimated costs of $3.5 billion including $240 million spent on antibiotics *(49)*. Despite the extensive clinical experience in the management of otitis media, there is no consensus regarding which antibiotics are most appropriate for initial or recurrent therapy, the optimal duration of therapy, or even whether antibiotics are of any significant benefit at all. The variation in management of otitis media is typified in an examination of the management of otitis media in nine countries in the mid-1980s *(50)*. In this study, antibiotics were used over a wide range (31–98%) of episodes with similar variation in the types of antibiotics used and duration of therapy.

Epidemiology

Because otitis media is a complication of URI, it has a peak incidence in the winter when colds are most likely to occur. Unlike sinusitis, which is more likely to affect adults, otitis media is predominantly a disease of younger children, with a peak incidence between 6 and 36 mo of age *(51)*. Otitis media occurs with varying frequency in children. In a large population study, it was found that during the first 3 yr of life about a third of children never had otitis media, another third had one or two episodes, and the remaining third had three or more episodes.

Otitis media occurs more often in males, children in lower socioeconomic groups, and in certain ethnic groups such as Native Americans. Because of differences in the mechanics of the posterior pharynx and eustachian tube, children born with craniofacial congenital abnormalities such as cleft lip/palate and those with trisomy 21 also are more likely to have otitis media as a complication of a cold.

Etiology

Otitis media arises from eustachian tube dysfunction that accompanies URIs or allergic rhinitis. Inflammation of the eustachian tube and middle ear results in tube occlusion and fluid accumulation in the middle ear space. Eustachian tube obstruction is more common in younger children because of less cartilage support of the tube, making collapse more likely. The Eustachian tube obstruction not only causes entrapment of existing fluid but also produces a negative pressure in the middle ear that results in additional fluid accumulation that characterizes serous otitis media. Contamination of this fluid with bacteria results in acute suppurative otitis media.

Suppurative otitis media is most often caused by the same organisms that result in sinusitis. Studies of middle ear aspirates suggest that *Streptococcus pneumoniae* is the most common bacterial cause of otitis media and is found in about 40% of effusions. *H. influenzae* accounts for approx another 20%. *B. catarrhalis* and *Staphylococcus aureus* each make up fewer than 10% of cases. In neonates, Gram-negative species also should be considered as potential etiologic agents.

Otitis media also may result from noninfectious obstruction of the eustachian tube. Allergic rhinitis, as noted previously, is one such mechanism. Other causes include enlargement of the adenoids and posterior pharyngeal tumors.

Treatment

The treatment of acute suppurative otitis media remains controversial. As indicated previously, there is a great deal of regional variability in the treatment methods used for this condition. However, a recent meta-analysis of six studies that investigated antibiotic therapy in children found no statistically significant benefits of antibiotics in children under the age of 2 *(52)*. However, there were several methodologic problems with many of these study that may limit the validity of these findings.

Other studies point out that otitis media may be overdiagnosed, especially in younger children, which complicates the evaluation of treatment effectiveness. Physicians' certainty about the diagnosis of otitis media was dependent on the patient's age. In a multinational study, it was found that physicians were certain of the diagnosis in only 58% of children under the age of 1 yr *(50)*. This increased to 66% in those between 1 yr and 30 mo of age and up to 73% in those over 30 mo of age. In this group,

regardless of age, antibiotic therapy did not appear to influence outcomes. However, as physician uncertainty about whether the child had suppurative otitis media was fairly high, it is likely that a large number of children without otitis media were included in the outcome measurement.

If antibiotics are selected for the management of acute suppurative otitis media, selection of an agent should provide coverage for the two most common organisms, *S. pneumoniae* and *H. influenzae.* Second, the duration of antibiotic treatment should be as short as possible to minimize the development of antibiotic resistance. In a meta-analysis of trials that compared short-duration antibiotic therapy with the traditional 10-d course, no benefit was found of using longer courses of treatment *(53).* A 5-d course of antibiotics should be sufficient for treatment.

In addition to short-course therapy, a single intramuscular dose therapy of ceftriaxone has been shown to have benefit equal to that of longer courses of amoxicillin *(54),* cefaclor *(55),* or trimethoprim–sulfamethoxasole *(56)* for the treatment of acute suppurative otitis media. Where antibiotic resistance to *S. pneumoniae* is high or where patient compliance is an issue, ceftriaxone may be a viable alternative.

The primary concern in the treatment of otitis media is a primary treatment failure, i.e. persistent illness or a early recurrence of disease following initial therapy of a new otitis episode *(57).* While a meta-analysis of 33 randomized trials supports initial antibiotic use (94% primary treatment success vs. 81% with placebo) *(58),* there were no significant differences in failure rates when comparing "standard" or first-line (penicillin, amoxicillin/ampicillin, erythromycin, and sulfamethoxazole) and "extended-spectrum" or second-line antibiotics or with duration of therapy. The only factor that appears to be consistently linked to a higher likelihood of a primary treatment failure is a child's age *(59,60),* with children younger than 2 yr of age of age having treatment failures in 26–37.5% of cases. For older children, treatment failures occur in 2–19% of episodes *(59,60).*

Also of concern is how to manage a new case of otitis media when a previous treatment failure has occurred. In a study that examined failure rates in new infections for children who had a previous treatment failure, there was no benefit of starting therapy with an extended-spectrum agent compared to "first-line" drugs. Thus it appears that in a case of previous treatment failure, new cases should be managed with narrow-spectrum agents such as amoxicillin or trimethoprim–sulfamethoxasole *(61).*

The use of second-line antibiotics when a first line agent will suffice creates two problems. First, in most cases the use of broad-spectrum drugs adds significant expense to therapy. Others have reported that use of second line agents compared to amoxicillin or trimethoprim–sulfamethoxasole adds 16% to the overall cost of the episode *(57).* Since the results of this study show comparable failure rates for first- and second-line antibiotics, there appears to be no justification for this additional cost.

Second, the injudicious use of broad-spectrum antibiotics may increase the potential for future development of antibiotic resistance. The overuse of antibiotics has been proposed as one reason for the observed growth in antibiotic resistance reported in common childhood organisms such as *Streptococcus pneumoniae.* Otitis media is a condition in which antibiotics are frequently prescribed for children and where broad-spectrum antibiotics may be used unnecessarily. Limiting the use of broad-spectrum

drugs to situations in which they are beneficial (i.e., managing the resistant case of otitis) may help reduce further development of drug resistance in children.

TONSILLITIS/PHARYNGITIS

Clinical Description

Sore throat is a common reason that patients consult with a physician. Most of these are viral infections related to upper respiratory infections, but about 20% are secondary to infection with Group A β-hemolytic streptococcus. The primary role of the physician is to differentiate streptococcal pharyngitis from viral illnesses. Despite the fact that most sore throats are due to viruses, often patients receive antibiotics for this condition even when streptococcal illness is not likely to be present *(62).* This leads to selection of resistant organisms as well as reinforcement of the desire for antibiotics on the part of the patient *(63).*

Because most patients with sore throats probably do not visit their doctor, it is difficult to state with any certainty how often sore throats occur in healthy populations. However, pharyngitis ranked fourth in the most common reasons for visits to family physicians in two different studies *(64,65).* Frequently antibiotics are prescribed for these conditions without evidence of a bacterial etiology.

Epidemiology

Both viral and Group A streptococcal pharyngitis have peak occurrences in the winter and early spring. Streptococcal infection, in particular, can be recognized in epidemic patterns frequently affecting groups that spend considerable time together in close quarters, such as day cares, schools, and places of employment. Strep throat also is related to patient age. While infection in the very young (< 1 yr old) is uncommon, the peak occurrence for strep throat is between 3 yr and 10 yr of age with diminished risk over the age of 20.

Etiology

The most common causes of pharyngitis are respiratory viruses. Adenovirus and the rhinoviruses account for approx 80% of cases of sore throat in children seen by physician *(66,67).* Coxsackievirus, herpesvirus, and Epstein–Barr virus can cause tonsillitis, but are less common than adenovirus *(68).* Adenovirus, coxackievirus, and Epstein–Barr can cause exudative pharyngitis that can mimic the appearance of streptococcal infection. Although exudative tonsillitis is thought to be a hallmark of group A streptococcal infection, this sign is actually present more often from adenovirus than from streptococcus.

Group A β-hemolytic streptococcus can cause an acute tonsillopharyngitis, but may colonize the oropharynx without symptoms. The asymptomatic carrier rate of Group A streptococcus ranges from approx 10% to 30% of healthy children, a rate that nearly matches the true infection rate *(69,70).* This means that in testing for group A streptococcus, positive tests are just as likely to occur from carriers of Group A streptococcus who have a concomitant virus as those actually infected with the organism. In contract to Group A streptococcal tonsillopharyngitis, treatment of the carrier state is not necessary and does not reduce symptoms or complications *(71).*

Another dilemma in identifying Group A streptococcus in patients with pharyngitis is the sensitivity of rapid group A antibody kits compared to a throat culture. Many studies have shown that a rapid test is less sensitive than the culture for identifying the presence of Group A streptococcus. Sensitivities for the rapid test compared to a standard blood agar culture vary considerably but are generally in the range of 60–70%. Studies also have demonstrated that in circumstances when the colony counts are low, rapid tests are more likely to miss the presence of Group A streptococcus. However, when the sero conversion of anti-streptolysin-O (ASO) titers is used as the gold standard for infection, rapid tests perform very well *(72).* It is likely that rapid tests miss patients who have a small number of organisms but who are likely to be colonized rather than infected. Thus, rapid testing may be more specific in identifying patients with actual streptococcus related disease than cultures that also identify those who are likely to be carriers. This suggests that follow-up throat cultures are not necessary and may actually confuse treatment decisions. Rapid streptococcus testing without culture also has been shown to be the most cost-effective approach to managing acute pharyngitis *(73).*

As indicated previously, reports regarding the role of *Chlamydia* and *Mycoplasma* indicate that these two organisms also may be associated with acute pharyngitis. However, there have been few treatment trials that demonstrate any benefit of treating non-Group A streptococcus with antibiotics that would treat either of these organisms. In a study using erythromycin to treat non-Group A streptococcal pharyngitis *(74),* patients who received placebo had the same speed of symptom resolution as those treated with active antibiotics.

Treatment

Group A β*-Hemolytic Streptococcal Tonsillopharyngitis*

Differentiating Group A streptococcal pharyngitis from viral disease is the most vexing problem in the management of acute sore throat. The clinical impression of the treating physician has been shown to be fairly inaccurate at making this differentiation *(72,75,76).* Several clinical decision rules have been evaluated to assist physicians in selecting patients for testing or treatment. One simple system that relied on the presence of fever, lymphadenopathy, exudative tonsillitis, and the absence of a cough improved the positive predictive value of a rapid Group A test significantly *(72).* Another study using expanded clinical criteria noted that unnecessary antibiotic prescribing would have been reduced 48% had a decision rule that looked at a wide variety of predictors been used to guide therapy *(75).*

Once Group A streptococcus has been implicated in the infection, the choice of antibiotic is controversial. With only scant evidence that treatment reduces the symptomatic period and a low risk of complications from untreated Group A streptococcal pharyngitis, some investigators suggest that antibiotic treatment carries more risks than not treating and encourages future health seeking and antibiotic expectations for future sore throats *(77).* However, formal decision analyses suggest that in cases of moderate probability of strep throat (40–85%) with symptom duration of 2 d or less, rapid streptococcus testing and treatment is beneficial *(78).*

Selection of an appropriate antibiotic and duration of therapy are important considerations in treating streptococcal pharyngitis. Penicillin V resistance in Group A strep-

tococcus as well as erythromycin resistance *(79)* has led to investigations of other drugs for management of strep throat. Because streptococcal pharyngitis is a self-limited problem even without antibiotic therapy, much of this resistance has been based on positive throat cultures following the termination of treatment. This may be misleading, as colonized patients may continue to harbor streptococcus even after therapy.

When drug failure rates are examined with penicillin, cultures remain positive in 11–45% of treated patients *(80,81).* However, single-dose therapy with amoxicillin at 40 mg/kg/d for 10 d appears to be very successful, resulting in excellent clinical responses and low rates (5–10%) of posttreatment carrier rates *(80,81).* Treatment with other agents such as azithromycin and clarithromycin produces no better results than amoxicillin or penicillin V *(82–84),* but at much greater expense.

Attempts at "short-course" therapy have been studied with azithromycin *(85).* Both short-course treatment with azithromycin and 10 d of cefaclor have exactly the same clinical cure rates (86%) by d 3 of therapy. However, patients treated with cefaclor were less likely to become recolonized with Group A streptococcus over the next 45 d than those treated with the short course of azithromycin (20% vs. 55%). As the significance of rapid recolonization is still unclear, short-course therapy with azithromycin or other antibiotics still requires additional investigation.

Group A Streptococcal Carriers

While the carrier rate does not require treatment *(71),* some clinicians attempt to eradicate those colonized by Group A streptococcus to prevent spread to other family members and close contacts. A regimen of intramuscular penicillin V plus oral rifampin has been shown to reverse the carrier status in 93% of patients treated *(86).* There have been no studies performed more recently that have explored whether this regimen remains effective with increased Group A streptococcus resistance to penicillin.

Non-Group A Streptococcal Pharyngitis

Despite evidence that *Chlamydia* and *Mycoplasma* may be associated with acute pharyngitis, there have been no studies that have shown a benefit from treatment of patients with non-Group A streptococcal pharyngitis with antibiotics. Studies with penicillin *(72),* which would not be expected to cover these agents, and macrolides *(74),* which would, have not shown any significant improvement over placebo. Until specific tests that can rapidly identify these organisms are developed that would allow for targeted treatment and studies can demonstrate that treatment reduces symptoms and complications, indiscriminate antibiotic therapy for non-Group A streptococcal pharyngitis should be avoided.

ACUTE BRONCHITIS

Clinical Description

Acute bronchitis is an inflammatory condition of the tracheobronchial tree usually associated with a generalized respiratory infection. Cough begins early in the course of the illness and is the most prominent feature of the condition. An initially dry cough may later result in sputum production which characteristically changes from clear to discolored in the later stages of the illness. The cough may last for a significant time.

Although the duration of the condition is variable, one study showed that 50% of patients had a cough for more than 3 wk and 25% had a cough for more than 4 wk *(87)*.

Patients with acute bronchitis usually have a viral respiratory infection with transient inflammatory changes that produce sputum and symptoms of airway obstruction. Acute bronchitis is essentially a diagnosis of exclusion. The history should include information on cigarette use, exposure to environmental toxins, as well as medication history (e.g., use of angiotensin converting enzyme inhibitors). The chronicity of the cough should be established to distinguish acute bronchitis from chronic bronchitis, as they have different treatments.

Both acute bronchitis and pneumonia can present with fever, constitutional symptoms, and a productive cough. Although patients with pneumonia often have rales, this finding is neither sensitive nor specific for the illness. When pneumonia is suspected on the basis of a presence of a high fever, constitutional symptoms, severe dyspnea, and certain physical findings or risk factors, a chest radiograph should be obtained to confirm the diagnosis.

Asthma and allergic bronchospastic disorders can mimic the productive cough of acute bronchitis. When obstructive symptoms are not obvious, mild asthma may be diagnosed as acute bronchitis. Further, because respiratory infections can trigger bronchospasm in asthma, patients with asthma that occurs only in the presence of respiratory infections resemble patients with acute bronchitis.

Asthma should be considered in patients with repetitive episodes of acute bronchitis. Patients who repeatedly present with cough and wheezing can be given full spirometric testing with bronchodilation or provocative testing with a methacholine challenge test to help differentiate asthma from recurrent bronchitis.

Finally, nonpulmonary causes of cough should enter the differential diagnosis. In older patients, congestive heart failure may cause cough, shortness of breath and wheezing. Reflux esophagitis with chronic aspiration can cause bronchial inflammation with cough and wheezing. Bronchogenic tumors may produce a cough and obstructive symptoms.

Epidemiology

Acute bronchitis in the otherwise healthy adult is one of the most common medical problems encountered in primary care *(5)*. The prevalence of acute bronchitis peaks in the winter and is much less common in the summer.

Etiology

Viral infection is considered the primary cause of most episodes of acute bronchitis. A wide variety of viruses have been shown as causes of acute bronchitis including influenza, rhinovirus, adenovirus, coronavirus, parainfluenza, and respiratory syncytial virus *(88)*. Nonviral pathogens including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (TWAR) have also been identified as causes *(89,90)*.

The etiologic role of bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* in acute bronchitis is unclear because these bacteria are common upper respiratory tract flora. Sputum cultures for acute bronchitis are therefore difficult to evaluate, as it is unclear whether the sputum has been contaminated by pathogens in the nasopharynx.

Treatment

Antibiotic treatment for acute bronchitis is quite common, with evidence indicating that 60–75% of adults visiting a physician for acute bronchitis receiving an antibiotic *(21,91).* Clinical trials of the effectiveness of antibiotics in treating acute bronchitis have produced mixed results. One reason for the lack of consensus is that in each of the nine trials different antibiotics were used and different outcomes were obtained. In an effort to quantitatively review the data, two different meta-analyses were recently conducted *(92,93).* In the Fahey et al. meta-analysis, resolution of cough was not affected by antibiotic treatment and neither was clinical improvement at reexamination. Importantly, the side effects of antibiotics were more common in the antibiotic groups compared to placebo. The Smucny et al. meta-analysis concluded that antibiotics may be modestly effective for a minority of patients with acute bronchitis although it is unclear which subgroups might benefit. The conclusion of both meta-analyses was that the benefits or antibiotics are marginal and are not useful for the general group of patients with acute bronchitis.

Recent data from clinical trials suggest that bronchodilators may provide effective symptomatic relief to patients with acute bronchitis *(94,95).* Treatment with bronchodilators demonstrated significant relief of symptoms including faster resolution of cough, as well as return to work. One study evaluated the effect of albuterol in a population of patients with undifferentiated cough and found no beneficial effect *(96).* Because a variety of conditions present with cough there may have been some misclassification in generalizing this to acute bronchitis.

Key Points

- Upper respiratory infections and acute bronchitis are common illnesses that account for a large proportion of total outpatient health care utilization, as well as nearly 75% of prescribed outpatient antibiotics.
- Evidence does not support the use of antibiotics for the common cold, acute bronchitis, initial cases of otitis media with effusion, and non-Group A streptococcal pharyngitis. These conditions are self-limited and currently are optimally treated with symptomatic medicines.
- Although the data are mixed regarding the utility of antibiotic treatment for acute sinusitis, otitis media, and Group A streptococcal pharyngitis, antibiotics may have some benefit. Short-course therapy with narrow-spectrum antibiotics appropriate for the likely pathogen is recommended.

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8
Diagnosis and Management of Pneumonia

Sundar Natarajan and Kimberly Rakes

INTRODUCTION

The diagnosis and management of pneumonia presents an opportunity to apply the principles of evidence-based medicine to a common health problem. Many complex issues arise while caring for patients with pneumonia, some of which have been formally addressed by controlled clinical studies. Current practice is based on an extensive accumulation of uncontrolled clinical experience rather than on proven principles. In this chapter we discuss common questions that arise during diagnosis and management of pneumonia.

Pneumonia occurs in approximately 10% of admissions to medical wards and remains a common cause of death. Although bacteria, viruses, and fungi are all frequent culprits, this chapter primarily addresses bacterial pneumonia, classified further into community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).

COMMUNITY-ACQUIRED PNEUMONIA

Epidemiology

Approximately 2–3 million cases of CAP occur each year in the United States with 25–30% of these requiring hospitalization *(1).* CAP is the sixth leading cause of death, accounting for approximately 45,000 deaths annually. The adjusted and unadjusted mortality rates have increased over the past few decades, owing in part to the increasing proportion of the population over the age of 65 and the fact that more of the population has other underlying medical conditions. The average mortality rate for CAP is 14% overall with the mortality rate among nonhospitalized patients being <1%. The incidence of CAP is higher in the winter months because of the greater predominance of *Streptococcus pneumoniae, Haemophilus influenzae,* and influenza viruses. A direct association with morbidity has been seen with increasing age, poor socioeconomic status, medical noncompliance, certain laboratory data, and certain comorbid illnesses. Leukocytosis, bacteremia, greater extent of radiographic changes, alcohol abuse, malignancies, immunosuppression, neurologic disease, congestive heart failure, diabetes, and history of previous pneumonia are associated with more severe outcomes. These factors should be taken into consideration when determining whether a patient should be hospitalized.

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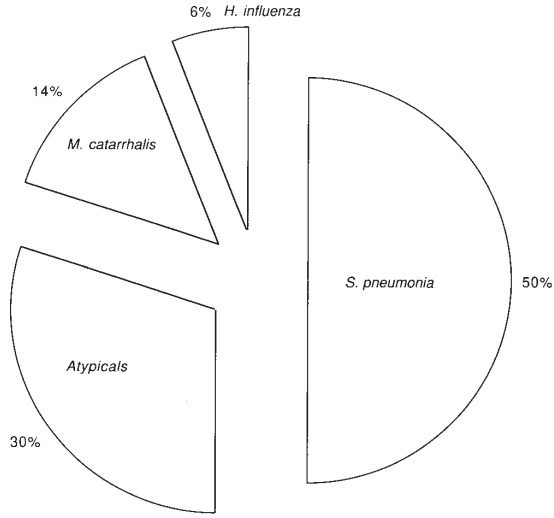

Fig. 1. Pathogen prevalence in community-acquired pneumonia.

Etiology

The most common cause of CAP is *S. pneumoniae,* followed by *Mycoplasma pneumoniae, Moraxella catarrhalis,* and *H. influenzae,* respectively, as shown in Fig. 1. While Fig. 1 shows the overall prevalence of pathogens in CAP, certain underlying medical conditions predispose patients to specific agents. Traditionally known as an etiologic agent in the elderly population, *S. pneumoniae* is also frequently seen in those with cardiovascular disease, chronic obstructive pulmonary disease, malignancies, asplenia, and human immunodeficiency virus (HIV). *Pneumocystis carinii* is still the most common cause of acute pneumonia in HIV. Although rare in healthy children and adults, *Legionella* spp. are a common cause of pneumonia in patients with organ transplants, renal failure, acquired immune deficiency syndrome (AIDS), and chronic lung disease. Seasonal variation occurs, with *S. pneumoniae* and *H. influenzae* occurring primarily in the winter months, while *Chlamydia pneumoniae* can be seen year round. Also seen is a predominance of *Legionella* pneumonia during the summer, mainly in the northeastern United States and Great Lakes region.

Diagnosis

Pneumonia, a frequent cause of acute respiratory symptoms, is one of the most common reasons for visiting a physician, representing more than 4% of all physician visits in 1994. Of those visits, 5% were attributed to CAP *(2).* Although pneumonia accounts for only a small fraction of diagnoses in patients with acute respiratory symptoms, to identify it accurately is crucial because of the high morbidity and mortality risks if left untreated. Inaccurately diagnosing other respiratory conditions as bacterial pneumonia (such as upper respiratory infections and bronchitis) and inappropriately treating them with antibiotics is an important reason for the rise in antibiotic resistance among common respiratory pathogens.

Clinical Signs and Symptoms

Symptoms can vary and are often subtle, particularly in the elderly. These may include cough, dyspnea, fever or hypothermia, chills, rigors, sweats, mental status changes as well as constitutional symptoms of fatigue, headache, myalgias, and anorexia. Physical exam may show diminished breath sounds, rales, wheezes, increased tactile fremitus, egophony, or whispering pectoriloquy, the latter being found more commonly with effusion or consolidation. In a prospective study, the most important signs for detecting pneumonia were unilateral rales and rales in the lateral decubitus position *(3).* Also, gastrointestinal signs and symptoms are commonly seen with *Legionella* sp. infections.

Laboratory and Imaging Tests

Individual symptoms and signs are not sufficiently sensitive or specific to diagnose pneumonia. Although several decision algorithms using different combinations of symptoms and signs are available, none of them are sufficient to confirm the diagnosis of pneumonia *(4).* For diagnostic certainty further testing is required.

1. Leukocyte count: Neutrophilia suggests bacterial infection. Leukocyte count may be low or normal in the elderly, immunocompromised patients, and those with overwhelming infections. Regardless of the absolute white count there is frequently a left shift.
2. Radiography: A chest radiograph is essential in confirming the diagnosis of pneumonia although it is not specific. It is particularly valuable in detecting parapneumonic effusions, abscesses, and cavities. It is also helpful to have baseline films to assess response to therapy, severity of disease, or sometimes even to suggest a specific pathogen, that is, cavitation with *Staphylococcus aureus, Klebsiella* sp., and anaerobes.
3. Sputum examination: A spontaneously expectorated sputum sample is ideal. It should contain leukocytes and fewer than 10 epithelial cells per low-power field on a Gram stain to be considered satisfactory. Inducing sputum with inhalation of a warm, saline aerosol or nasal tracheal suction can be helpful, particularly when tuberculosis or *Pneumocystis* infection is suspected. A properly stained slide is also important to make empiric therapy more pathogen specific.
4. Cultures: In patients with a productive cough, sputum should always be cultured and results compared with those of a simultaneous Gram stain. Sputum should not be cultured anaerobically because contaminating pharyngeal organisms may produce misleading results. Blood cultures are often positive in patients with pneumococcal pneumonia and should be drawn as soon as possible, preferably before antibiotics are given. Treatment should never be withheld while trying to obtain a specimen. Pleural fluid cultures may also be helpful when a significant effusion is present. Of note, cultures are frequently negative for atypical organisms unless specific media are used.
5. Invasive procedures: Transtracheal aspiration, transthoracic needle aspiration, bronchial brushings, bronchoalveolar lavage, transbronchial biopsy, and open lung biopsy may be required to diagnose severe pneumonias especially in patients who are immunocompromised, fail to respond to therapy, or are likely to have a nonbacterial etiology for the infiltrate. These are usually not done initially, but are reserved for patients who are not improving clinically on appropriate empiric therapy.
6. Other tests: Other laboratory tests might include an HIV test, particularly in patients between the ages of 15 and 54 *(5).* Serologic or urinary antigens may be helpful in identifying *Legionella.* Serum sodium may also be abnormal in patients with *Legionella* pneumonia. In the future, polymerase chain reaction (PCR) may help diagnose atypical pneumonia, particularly if the patient is severely ill and cultures continue to be negative.

Prognosis and Management Based on Risk Level

Risk Factors for Poor Outcomes

Several factors associated with poor prognosis have been identified *(6–8).* These include age > 65 yr; comorbid conditions; hospitalizations within the previous year; and clinical signs such as tachypnea, hypoxia, fever > 38.3°C, low blood pressure, and coexisting extrapulmonary infections. Among etiologic agents, *S. pneumoniae, Legionella* sp., and *S. aureus* are associated with poorest outcomes.

Algorithm for Management

Treatment of patients with pneumonia varies by geographic region and by practitioner. The decision to hospitalize patients has often depended on the physician's subjective impression *(9,10).* Despite excellent response to antibiotics, high morbidity and mortality rates continue to be associated with pneumonia. Therefore, physicians tend to overestimate mortality risk, leading to frequent hospitalizations. Hospitalization in turn leads to greater use of medical resources, which may be inappropriate. Despite considerable variations in antimicrobial prescription patterns and costs, it has been shown that there are no significant differences in clinical outcomes between patients treated at institutions with high costs and those with lower costs *(11).*

Accurate prognostic models allowing physicians to identify low-risk patients may help physicians estimate patient risk and could lead to superior decision making. The pneumonia Patient Outcomes Research Team (PORT) *(12)* developed a prediction rule for accurately identifying patients with CAP who are at low risk of dying within 30 d of presentation. This rule also has good predictive accuracy for other clinically relevant major outcomes. The prediction rule assigns points based on age and the presence of coexisting disease, abnormal physical findings, and abnormal laboratory findings at presentation. The patients in the lowest risk classes have been shown to have minimal risk for death and other adverse outcomes. Figure 2 shows the algorithm for identifying patients at low risk.

Patients can be identified as being at the lowest risk (class I) based on the history and physical examination alone. Patients at higher risk can be categorized into classes II–V based on characteristics such as demographic factors; residence; comorbidities; and findings on physical examination, laboratory studies, and radiography. A point scoring system for assignment to classes II–V is shown in Tables 1 and 2.

The observed mortality rates for the different classes and the recommendations for site of care are shown in the Table 3.

Treatment

Initial treatment of pneumonia is usually empiric antibiotic therapy; however, results of a properly performed Gram stain may allow more specific therapy *(13).* If a specific etiologic agent is subsequently identified, antimicrobial therapy can be adjusted accordingly. The otherwise healthy patient with CAP will usually have subjective improvement and resolution of fever 1–3 d after initiation of therapy *(14).* There may be delayed clearing of the chest radiograph which should not be a concern in a clinically improving patient, sometimes taking 7–12 wk to resolve completely. If changes persist, further evaluation for the presence of a foreign body or obstructive lesion may be necessary.

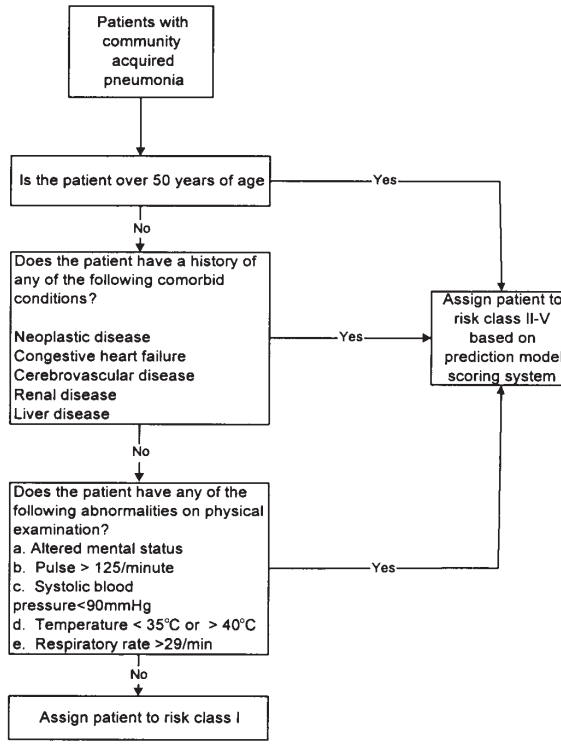

Fig. 2. Algorithm to identify low-risk patients with community-acquired pneumonia.

Therapy for CAP can be categorized into general supportive measures, empiric management, and agent-specific treatment.

General Supportive Measures

Although no data are currently available concerning supportive care, common practice is to use oxygen supplementation and hydration for most hospitalized patients. In some instances it may be beneficial to also use bronchodilators and chest percussion with postural drainage, particularly if evidence of consolidation by radiograph or physical examination exists.

Empiric Treatment

Empiric treatment for suspected bacterial infection should be directed against the most likely pathogens and should be started promptly after appropriate cultures are obtained. If a diagnostic Gram stain cannot be obtained, the treatment is based on the setting, the health status of the patient, other comorbidities, and availability of social support. For example, otherwise healthy patients who are treated on an outpatient basis usually need only one oral agent.

Tables 4 and 5 contain some of the current recommendations for both inpatient and outpatient treatment. One must keep in mind, however, that pneumonia patients with

Table 1
Point Scoring System for Classifying High-Risk CAP Patients

Patient Characteristics	Points Assigned[a]
A. Demographic factors	
Age: Males	Age in years
Females	Age in years – 10
Nursing home resident	+ 10
B. Comorbid diseases	
Neoplastic disease	+ 30
Liver disease	+ 20
Congestive heart failure	+ 10
Cerebrovascular disease	+ 10
Renal disease	+ 10
C. Physical examination findings	
Altered mental state	+ 20
Respiratory rate ≥ 30/min	+ 20
Systolic blood pressure < 90 mmHg	+ 20
Temperature < 35°C or ≥ 40°C	+ 15
Pulse ≥ 125/min	+ 10
D. Laboratory findings	
pH < 7.35	+ 30
BUN > 10.7 mmol/L	+ 20
Sodium < 130 mHq/L	+ 20
Glucose > 13.9 mmol/L	+ 10
Hematocrit < 30%	+ 10
PO_2 < 60 mm Hg[2]	+ 10
Pleural effusion	+ 10

[a] A total point score for a given patient is obtained by adding the patient's age in years (age – 10 for females) and the designated points for each applicable patient characteristic.

[b] Oxygen saturation < 90% also was considered abnormal.

Table 2
Identification of Risk Classes Among Patients with CAP

Risk	Risk Class	Based on Algorithm
Low	I	No predictors
	II	≤ 70 Total points
	III	71–90 Total points
Moderate	IV	91–130 Total points
High	V	> 130 Total points

Table 3
Mortality and Recommendations for Site of Care for CAP

Risk Class	No. of Points	Mortality %	Site of Care
I	No predictors	0.1	Outpatient
II	< 70	0.6	Outpatient
III	71–90	2.8	Inpatient (briefly)
IV	91–130	8.2	Inpatient
V	> 130	29.2	Inpatient

Table 4
Recommendations for Empiric Treatment for Outpatients

Scenario/Setting	Recommendation	Rationale
Healthy with few or no risk factors	(a) Macrolide (not erythromycin if *H. influenzae* suspected), fluoroquinolone (with increased activity against *S. pneumoniae*), or doxycycline *(16)*	Maximize coverage against both typical and atypical organisms
	(b) The least expensive β-lactamase *(17)*	Typical and atypical organisms distinct. This is the treatment for typical organisms.
	(c) Erythromycin. Add trimethaprim–sulfamethoxazole, second- or third-generation cephalosporin, or use a new macrolide if the patient is older or has minor health problems *(18)*	Difficult to differentiate typical vs atypical pneumonia; therefore recommend broader coverage.
Suspected aspiration	Amoxicillin/clavulanate *(16)*	Increases anaerobic coverage

Table 5
Recommendations for Empiric Treatment of Hospitalized Patients with CAP

Scenario/Setting	Recommendation	Rationale
Mild to moderately ill	β-Lactam ± macrolide OR fluoroquinolone *(16)*	Broaden coverage for more severely ill patients
Moderately to severely ill	(a) Macrolide PLUS trimethoprim–sulfamethoxizole, or antipseudomonal third-generation cephalosporin *(18)*	Broaden coverage for more severely ill patients, including two agents that cover *Pseudomonas* sp.
	(b) Either macrolide + third-generation cephalosporin or other antipseudomonal agents such as imipenam/cilastatin, ciprofloxacin *(16)*	
Suspected aspiration	Fluoroquinolone PLUS clindamycin or metronidazole or β-lactam/β-lactamase inhibitor *(16)*	Broadens coverage for anaerobes

chronic pulmonary disease, alcoholism, immunocompromised states, and possible aspirations must sometimes be treated differently, as the etiologic organisms may be different. For patients in whom a diagnostic Gram stain can be obtained, the treatment is based on those results. Once cultures are obtained, more specific treatment can be initiated.

A key factor to keep in mind is the local resistance pattern(s) of the suspected organism(s). While resistance varies among organisms, *Streptococcus pneumoniae* has had an alarming pattern of increasing resistance over the last 20 yr *(15),* another reminder that antibiotics must be used with caution and only when clinically indicated. Finally, it is prudent to remember that empiric therapy should also cover atypical organisms.

Outpatient Treatment

Although there are differing opinions on empiric coverage in the outpatient setting, most physicians follow the Infectious Disease Society of America (IDSA) guidelines which recommend treatment with a macrolide, fluoroquinolone, or doxycycline in individuals without significant risk factors. Others, however, feel that a β-lactamase agent may be used for "typical" bacterial pneumonia *(13)* and erythromycin for "atypical" infections. High-risk patients in the latter grouping may benefit from the addition of trimethoprim–sulfamethoxizole or with the use of second- or third-generation cephalosporins. Most agree that amoxicillin/clavulanate should be used if aspiration is suspected to increase anaerobic coverage. Table 4 shows current recommendations and rationale for specific scenarios or settings.

Inpatient Treatment

While outpatient management recommendations differ among authors, inpatient management is more uniform. Mild to moderately ill patients are usually treated with β-lactams with or without a macrolide or with a fluoroquinolone alone. For moderately to severely ill patients, double coverage of pseudomonal infections is necessary and can be achieved with a macrolide plus trimethoprim–sulfamethoxazole, or certain third-generation cephalosporins, or another antipseudomonal agent. As with outpatient pneumonia, patients hospitalized for suspected aspiration should have broadened coverage.

To increase anaerobic coverage most sources recommend a fluoroquinolone and clindamycin, metronidazole, or a β-lactam with a β-lactamase inhibitor. Table 5 shows current recommendations and rationale for empiric treatment of hospitalized patients with CAP.

Agent-Specific Treatment

Agent-specific therapy is the most effective and appropriate means of treating pneumonia and decreases the chance of treatment failure and future emergence of antibiotic resistance. Table 6 contains the current accepted recommendations for the common organisms encountered in CAP.

NOSOCOMIAL/HOSPITAL-ACQUIRED PNEUMONIA

Defined as pneumonia acquired while hospitalized, nosocomial pneumonia is a serious threat to patients who are already ill. Nosocomial pneumonia accounts for one half

Table 6
Recommendations for Agent-Specific Therapy of CAP

Organism	Drug of Choice	Alternate Agents	Comment
S. pneumonia	Penicillin, amoxicillin Cephalosporin (second- or third-generation)	Cephalosporins, macrolides, doxycyclines, vancomycin, fluoroquinolone	For strains with intermediate levels of resistance: high-dose penicillin, cefotaxime, or ceftriaxone. For highly resistant strains: vancomycin
H. influenzae	Cephalosporin (second or third generation) Trimethoprim–sulfamethoxazole Doxycycline	Fluoroquinolone, azithromycin	β-Lactamase production with amoxicillin resistance in 20–30% of strains
S. aureus	Oxacillin or nafcillin with or without gentamicin or rifampin	Cefuroxime or cefazolin, vancomycin, clindamycin, TMP-SMZ, fluoroquinolone	Methicillin resistance rare in community-acquired strains
Anaerobes	Clindamycin	Penicillin plus metronidazole, β-lactam, β-lactamase inhibitor, penicillin or amoxicillin	Published experience limited except for penicillin and clindamycin
Gram-negative bacilli	Cephalosporin (second- or third-generation) with or without aminoglycoside	Fluoroquinolone, impenem, antipseudomonal penicillin, aztreonam	In vitro sensitivity tests required
Legionella species	Erythromycin, ciprofloxacin	Clarithromycin or azithromycin or doxycycline	Experience extensive only with erythromycin. Rifampin often added.
Mycoplasma pneumoniae	Doxycycline, erythromycin	Clarithromycin or azithromycin, fluoroquinolone	
Chlamydia pneumoniae	Doxycycline, erythromycin	Clarithromycin or azithromycin, fluoroquinolone	

Table 7
Risk Factors for Hospital-Acquired Pneumonia

A. Host-related
1. Age
   - Persons >65 yr of age

2. Underlying illnesses (such as):
   - Chronic obstructive pulmonary disease
   - Immunosupression
   - Diabetes Mellitus
   - Depressed consciousness
   - Surgery (thoracic/abdominal)
   - Malnutrition

B. Device-related
   - Endotracheal intubation and mechanical ventilation
   - Nasogastric tube (NGT) placement and enteral feeding
   - Contaminated aerosol from devices

C. Personnel or procedure-related
   - Cross-contamination by hands
   - Antibiotic administration

of deaths in patients with nosocomial infections and is the second most common infection acquired by hospitalized patients, behind only urinary tract infections. Although all hospitalized patients are at risk for HAP, mechanical ventilation and prolonged hospitalizations make patients more susceptible, with the former increasing the incidence as much as 6- to 20-fold. It is frequently discovered after a patient becomes febrile, hypoxic, or has altered mental status. While the physical exam findings in both community- and hospital-acquired pneumonia are similar, their etiologic organisms frequently are not. A much higher incidence of Gram-negative organisms and *S. aureus* exists, but a significant percentage of HAP is still due to *H. influenzae* and *S. pneumoniae* in mild to moderately ill patients. Initial treatment of HAP is usually empiric and is determined, in part, by risk factors. Common risk factors for HAP are shown in Table 7.

Empiric therapy usually consists of double coverage for *Pseudomonas* sp., which can be the most lethal culprit in this setting. Based on severity of HAP and the presence of other risks leading to higher probability of infection with certain particular organisms, antibiotics can be tailored appropriately *(19,20).* Severe HAP is defined as HAP requiring admission to the intensive care unit, concomitant respiratory failure, rapid radiographic progression, and evidence of sepsis. The recommendations for empiric therapy of HAP are shown in Table 8.

PREVENTION OF PNEUMONIA

Preventive measures for pneumonia can be classified in two ways. The more common method of prevention consists of vaccinations directed toward influenza virus and pneumococci which work by enhancing host resistance once the organism is encoun-

Table 8
Empiric Therapy Recommendations for HAP

Empiric Scenario	Recommendations	Rationale
Mild to moderate HAP without risk factors OR Severe HAP without risk factors and early onset *(21,22)*	• Second-generation cephalosporin, OR • Nonpseudomonal third-generation cephalosporin, OR • β-Lactam/β-Lactamase inhibitor	High frequency of *H. influenzae, S. pneumoniae,* or *S. aureus* infection
Mild to moderate HAP with PCN allergy	• Fluoroquinolone OR • Clindamycin and aztreonam	Good coverage against *H. influenzae, S. pneumoniae,* or *S. aureus* infection
Mild to moderate HAP with risk of infection with anaerobes	• Add clindamycin to above OR • β-Lactam/β-Lactamase inhibitor alone	Provide better coverage against anaerobes
HAP with MRSA likely	• Add vancomycin	Reliable and effective treatment of MRSA
HAP with *Legionella* infection likely	• Add erythromycin or rifampin	
Severe HAP with risk factors or late onset (> 5 d after hospitalization)	• (Aminoglycoside or ciprofloxacin) + (antipseudomonal PCN or β-lactam/β-lactamase inhibitor or ceftazidime or cefoperazone or imipenam or aztreonam)	

PCN = penicillin
MRSA = methicillin-resistant *Staphylococcus aureus*

tered. Influenza vaccines are recommended for all individuals over the age of 65: for subjects at risk for adverse outcomes, including any immunocompromised state, such as heart disease, lung disease, malignancy, or diabetes: and for health care workers exposed to the virus. This vaccination works both by reducing the incidence of influenza pneumonia and by decreasing secondary bacterial pneumonia from superinfection. The currently available 23-valent pneumococcal vaccine is active against almost 90% of serotypes causing disease and some related serotypes. The increasing prevalence of antibiotic resistance among pneumococcal isolates makes immunization of high-risk individuals a particularly important intervention.

The second method of prevention relates only to hospital-acquired pneumonia and is directed at decreasing the chance of an organism reaching a susceptible host environment *(23,24).* This includes strategies to maintain gastric acidity and prevent aspiration, control spread of infection by washing hands properly, using gloves and face masks, and utilizing negative pressure isolation rooms.

ISSUES IN ANTIMICROBIAL TREATMENT

1. Bactericidal vs bacteriostatic antibiotics: Based on whether they kill or inhibit growth, antimicrobial agents are traditionally classified as bactericidal or bacteriostatic, respectively. This classification is an oversimplification, as an antimicrobial agent may be partially bactericidal or bacteriostatic for one species of bacteria and fully bactericidal for another. General dogma is that pneumonia should be treated only with bactericidal drugs. The rationale given to support this is that colonies of bacteria within the consolidated area are protected from host defenses, especially neutrophils. In other body sites these neutrophils would usually eliminate organisms inhibited by bacteriostatic antibiotics.
2. Single vs multiple antimicrobial therapy: Pneumonia is generally regarded as being easy to treat. Therefore, in most cases acceptable cure rates can be obtained using a single antibiotic. However, nosocomial pneumonia, especially in critically ill patients, usually requires combination antibiotic therapy. The rationale for this is that antibiotics that act by different mechanisms could serve to expand antibiotic coverage, reduce toxicity from lower individual doses of the drug, or act synergistically and potentially lower the development of antibiotic resistance. The most work in this area has examined only immunocompromized hosts, and it may not be appropriate to extrapolate that evidence to other settings. Among the different agents, aminoglycosides have been shown to be particularly effective in empirically treating severe nosocomial pneumonias and in treating pneumonia due to *Pseudomonas aeruginosa, Acinetobacter* sp., and β-lactamase producing Gram-negative organisms.
3. Optimal duration of treatment of antibiotics: Early experience established that pneumonia could not be cured by short courses that may have been appropriate to cure other infections such as urinary tract infections. Trials of longer duration were more successful, eventually leading to the widely followed practice of treating pneumonia for 2 wk, although there is no evidence to support this. The Pneumonia Patient Outcomes Research Study showed that it remains common practice today despite the fact that more than half of all cases could be reliably cured by a shorter duration of treatment. It has been felt, however, that *Chlamydia* pneumonia should be treated for 3 wk and *Mycoplasma* infections for 2 wk with either doxycycline or erythromycin. However, the newer macrolides can be given for shorter periods, 5 d for azithromycin and 10 d for clarithromycin *(25)*.

CONCLUSION

Pneumonia, both community and hospital acquired, is a common and potentially lethal disease. While treatment is usually empiric for both, recognizing the most likely pathogen involved is important so that appropriate treatment may be initiated as soon as possible. Equally important is the identification of the setting in which the patient became ill and any risk factors, as these may change the initial therapy. Since antimicrobial resistance continues to rise, use of antibiotics only when clinically indicated is imperative. Finally, preventive measures, such as vaccinations and attention to cleanliness and sterilization, must be implemented to ensure that patients have the lowest possible risk for infection.

Key Points

- Pneumonia is common and can be fatal, particularly in high-risk patients. Patients with pneumonia can be easily risk stratified into risk classes based on readily available clinical information and further management based on risk class.
- Community- and hospital-acquired pneumonia involve different organisms. Empiric treatment directed at the most likely pathogens should be promptly started based on the setting, patient health status, risk factors for poor outcomes, and other comorbidities.
- Therapy guided by culture results is optimal, leading to better patient response and decreased antibiotic resistance. Several choices for effective targeted treatment are available.
- Because of the increasing problem of antibiotic resistance emphasis should be placed on preventive measures such as vaccination, which should be implemented in all eligible patients.

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9
Tuberculosis

Martin E. Evans

EPIDEMIOLOGY

In 1990, approx 1.7 billion persons, or one-third of the world's population, was infected with *Mycobacterium tuberculosis (1).* Tuberculosis (TB) remains the largest cause of death from infectious diseases, with 3 million deaths worldwide each year *(2).* The mortality rate has steadily declined since it peaked at 400/100,000 in 1750, in association with migration to cities during the Industrial Revolution *(3).* When streptomycin was introduced in 1946, the mortality rate was 33/100,000. By 1993, the mortality rate in the United States had declined to less than 1/100,000 *(4).*

However, the emergence of resistant TB raises new concerns about the ability to respond effectively to the epidemic. Resistance is usually determined in the mycobacteriology laboratory by plating a known inoculum and comparing growth on antibiotic-free agar with that on agar containing critical concentrations of antibiotic. The threshold concentration of antibiotic that inhibits growth is correlated with achievable serum levels of the antibiotic using standard dosing *(5). M. tuberculosis* may be resistant to any of the major antibiotics used to fight this infection, including isoniazid (INH) or rifampin. The term multidrug-resistant tuberculosis (MDR-TB) usually refers to bacteria resistant to both INH and rifampin.

Drug resistance can be primary or acquired. In the former, the patient is infected with a resistant organism even though the patient has never received therapy. In the latter, the patient's initially sensitive organism becomes resistant after exposure to antimicrobials. The emergence of drug resistance is most often the result of inappropriate use of antituberculous therapy for the patient with initially drug-susceptible infection. From 1994 through 1997 in the United States, the prevalence of primary resistance to one or more drugs was 12.3% of total cases and the prevalence of acquired resistance was 23.6% of total cases. The prevalence of primary and acquired MDR-TB was 1.6% and 7.1%, respectively. Drug resistance was more common in persons coinfected with human immunodeficiency virus (HIV), between ages 15 and 24 yr, who were Asian or Pacific Islanders, or were foreign born *(6).* The risk of MDR-TB was 10–50 times higher for racial or ethnic minorities than for Caucasians. Globally, during the same years, the median rate of primary resistance was 9.9% (range 2–41%). If the patient had received an antituberculous drug for at least 1 mo, the prevalence of resistance

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increased on average to 36%. The median prevalence of primary MDR-TB worldwide was 1.4% and that of acquired resistance was 13% *(7)*.

Today the expected cure rate for disease caused by drug-sensitive *M. tuberculosis* approaches 100% *(8)*. The presence of drug resistance, however, leads to a greater chance of treatment failure. In recent trials, the presence of drug resistance decreased clinical cure rates to 89% *(9)*. Resistance to multiple drugs, especially to both INH and rifampin (MDR-TB), markedly reduced the chance for cure. Patients admitted to the National Jewish Medical and Research Center in Denver with MDR-TB, for instance, had a sputum conversion rate of only 65% and a cure rate of only 56% even with the best therapy available *(10)*. The prognosis of MDR-TB is even worse in patients coinfected with HIV. In eight different outbreaks, the average mortality rate was 78% with a median survival of only 5.6 wk after diagnosis *(11)*.

MDR-TB was recognized as a problem in the United States after outbreaks occurred in hospitals and correctional systems *(11)*. The outbreaks were unusual because of the large number of patients involved, the association with HIV infection, a short clinical course, and a high mortality rate. Some of the strains reported, such as strain "W" from New York City, were resistant to as many as eight drugs (isoniazid, rifampin, streptomycin, ethambutol, ethionamide, kanamycin, capreomycin, and ciprofloxacin) *(12)*. This and related strains have spread throughout the United States.

Additional outbreaks of MDR-TB have been reported in a medical examiner's office, after use of a contaminated bronchoscope, and after a long airplane flight *(13–15)*. In one hospital, the skin test conversion rate among healthcare workers rose more than 40-fold on wards that housed a patient with unsuspected pulmonary MDR-TB. One health care worker who contracted TB died *(16)*.

RESISTANCE

M. tuberculosis becomes resistant to antibiotics through spontaneous mutations in the chromosome. INH resistance is associated with deletions or mutations in the *katG* gene. This gene encodes a catalase-peroxidase enzyme, which activates INH *(17)*. The *inhA* gene also may be involved with resistance to INH as well as to ethionamide *(17)*. The exact mechanism of resistance with the *inhA* gene has not been described. Substitution of leucine for serine at position 531 in the *rpoB* gene confers resistance to rifampin. This mutation is also associated with high-level rifabutin resistance *(18)*. Resistance to fluoroquinolones is due to point mutations in the *gyrA* gene *(19)*. None of the known genes are linked, so resistance to one antibiotic usually does not confer resistance to another unrelated drug *(20)*.

Mutations leading to rifampin resistance occur at a rate of approx 10^{-8}. Mutations leading to INH, streptomycin, ethambutol, kanamycin, or aminosalicylic acid (PAS) resistance occur at a rate of approx 10^{-6} and mutations to ethionamide, capreomycin, cycloserine, or thiacetazone occur at a rate of approx 10^{-3} *(21)*. Resistance to fluroquinolones occurs with a frequency of 10^{-8} *(19)*. Resistance to two antibiotics, such as rifampin and INH, would be expected to occur at the multiplicand of the two resistance frequencies (i.e., $10^{-8} \times 10^{-6}$ or 10^{-14}). Because tuberculous cavities may contain 10^9 organisms *(36)*, any patient with cavitary TB carries approx 1000 organisms with primary resistance to INH and 10 organisms with primary resistance to rifampin before any therapy. Since few, if any, bacteria are resistant to both drugs, however, the proba-

bility of cure using both drugs is high because INH would kill the rifampin-resistant bacteria and rifampin would kill the INH-resistant bacteria. If, however, the patient were infected with INH-resistant *M. tuberculosis,* the majority of organisms in the cavity would be resistant to INH, and a regimen of INH and rifampin would, in effect, be single-drug therapy with rifampin alone. Rifampin resistance would develop among the INH-resistant population at a frequency of 10^{-8}. The patient might improve initially while rifampin kills the majority of the bacteria, but then strains resistant to both drugs would emerge, and the patient would relapse.

Physician behavior can lead to drug resistance *(22).* In 1977, Byrd and co-workers assessed the management of TB by nonpulmonary physicians and concluded that 73% of the patients had been treated inappropriately *(23).* The most common errors were the use of inadequate or excessive drug doses and the use of a single drug to treat bacteriologically proven disease. In 1993, similar problems were noted in an analysis of the previous management of patients with MDR-TB referred to the National Jewish Medical and Research Center in Denver. In this study, common errors leading to MDR-TB included (1) failure to obtain susceptibility testing, (2) failure to start an adequate initial regimen, (3) failure to modify the regimen when the susceptibility of the organism changed, and (4) failure to use directly observed therapy (DOT) *(24).* In a recent survey of TB management practices in Kentucky, investigators found that TB was diagnosed by culture in only 66% of patients (thus, no susceptibility data were obtained in the remaining 34% of patients), 12 different regimens were used to treat the patients, monitoring of bacteriologic cure was appropriate in fewer than 65% of cases, and DOT was used in only 38% of patients *(25).* Reports from other countries have documented similar problems.

TREATMENT OF DRUG-SENSITIVE TB

General

Streamlined yet efficacious regimens for the treatment of TB have been developed to improve compliance and cure rates. The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) currently recommend three options for the initial treatment of TB *(4,22).* The first, and simplest, is to begin with INH, rifampin, and pyrazinamide. The two key drugs in the regimen are INH and rifampin. Relapse rates are 0–4% with susceptible *M. tuberculosis,* 2–7% with INH-resistant bacteria, and up to 72% with rifampin resistance *(26).* The inclusion of pyrazinamide is essential for the rapid sterilization of cavities, but the ability of pyrazinamide to prevent the emergence of resistance is low. For this reason, a fourth drug (ethambutol or streptomycin) is recommended if resistance to INH in the community is ≥4% *(27).* In one study, only 3.5% of isolates were resistant to a drug in the regimen including ethambutol, and only 4.7% of isolates were resistant to a drug in the regimen including streptomycin *(28).* The fourth drug can be stopped as soon as the laboratory confirms that the isolate is susceptible to INH and rifampin. Pyrazinamide should be continued for 2 mo and INH and rifampin for a total of 6 mo.

The second recommended option is to treat with four drugs daily for 2 wk followed by all four drugs for another 6 wk on a twice per week schedule. If the organism is sensitive to INH and rifampin, the other drugs can be stopped and INH and rifampin con-

tinued for the remaining 4 mo of short-course therapy. The third option is treat with INH, rifampin, pyrazinamide, and ethambutol or streptomycin three times per week for the entire 6 mo. Recommended doses of each drug and potential side effects are listed in Tables 1 and 2.

The use of fixed-dose combinations of antituberculous drugs has been proposed as one method to prevent drug resistance *(29).* Rifamate™ (Hoechst Marion Roussel, Kansas City, MO) containing 150 mg of INH and 300 mg of rifampin per tablet, and Rifater™ (Hoechst Marion Roussel) containing 50 mg of INH, 120 mg of rifampin, and 300 mg of pyrazinamide per tablet are currently the only two products on the market. The idea is that patients taking fixed-dose combinations would not be able to stop a single agent without stopping therapy completely. Thus selection of organisms resistant to a single antibiotic is unlikely. However, because multiple tablets need to be ingested to achieve the necessary dose, there is the possibility that a patient may not take the full complement of pills and thus be underdosed. This might allow the emergence of resistance to all agents simultaneously.

Rifapentine (Priftin™, Hoechst Marion Roussel) has recently been marketed. This antibiotic has a half-life of >13 h, allowing it to be administered on a twice weekly or once weekly basis in place of rifampin. Patients have been treated with a regimen of INH, pyrazinamide, and ethambutol given daily plus rifapentine (600 mg) given twice weekly for 2 mo, followed by INH (900 mg) and rifapentine (600 mg) given weekly for 4 mo. The sputum conversion rate was 87% for this regimen compared to the standard rifampin-containing regimen, but relapse rates were higher (10% vs 5%, respectively) *(30).*

When difficulties arise with antituberculous therapy, the treatment regimens may need to be adjusted. This is difficult with fixed-dose combinations. It is easier to identify the drug responsible for adverse reactions if drugs are being administered individually. If the primary problem is drug toxicity, it is safe to change or add a single agent as long as the patient is being treated with at least two drugs to which the mycobacterium is still sensitive. It is imperative, however, never to add a single agent to a regimen where the patient is not improving or worsening clinically. Clinical failure implies that the organism is resistant to most, if not all, agents being used. If only a single new agent is added, the probability that the organism will become resistant to the new agent is high.

Considerations for Patients Coinfected with HIV

The immunosuppression due to HIV infection impairs the host response to infection with *M. tuberculosis,* and infection with *M. tuberculosis* accelerates the progression of HIV disease. Coinfection results in a higher relapse rate after treatment and a TB mortality rate that is four times that of persons not infected with HIV *(31).* Eleven percent of European HIV-infected patients and up to 75% of African patients with HIV infection may be coinfected with TB. In the United States, the incidence of TB in AIDS patients may be 200–800 times greater than that of the general population *(32).*

Treatment of TB in HIV-infected persons can be very complex for a number of reasons. First, drug resistance is more common in HIV-infected patients than in uninfected persons. Resistance rates among HIV-infected and noninfected patients were 11.3% and 5.5% for isoniazid, 8.9% and 1.6% for rifampin, 5.1% and 1.8% for pyraz-

Table 1
Dosage Recommendations for the Initial Treatment of TB Among Children and Adults

	Dosage					
	Daily		Two Times/wk		Three Times/wk	
Drugs	Children	Adults	Children	Adults	Children	Adults
Isoniazid	10–20 mg/kg Max 300 mg	5 mg/kg Max 300 mg	20–40 mg/kg Max 900 mg	15 mg/kg Max 900 mg	20–40 mg/kg Max 900 mg	15 mg/kg Max 900 mg
Rifampin	10–20 mg/kg Max 600 mg	10 mg/kg Max 600 mg	10–20 mg/kg Max 600 mg	10 mg/kg Max 600 mg	10–20 mg/kg Max 600 mg	10 mg/kg Max 600 mg
Pyrazinamide	15–30 mg/kg Max 2 g	15–30 mg/kg Max 2 g	50–70 mg/kg Max 4 g	50–70 mg/kg Max 4 g	50–70 mg/kg Max 3 g	50–70 mg/kg Max 3 g
Ethambutol	15–25 mg/kg Max 2.5 g	15–25 mg/kg Max 2.5 g	50 mg/kg Max 2.5 g	50 mg/kg Max 2.5 g	25–30 mg/kg Max 2.5 g	25–30 mg/kg Max 2.5 g
Streptomycin	20–30 mg/kg Max 1 g	15 mg/kg Max 1 g	25–30 mg/kg Max 1.5 g	25–30 mg/kg Max 1.5 g	25–30 mg/kg Max 1 g	25–30 mg/kg Max 1 g

Data from ref. *34*.

Table 2
Drugs Used for Tuberculosis

Antibiotic	Usual Dose	Major Side Effects (1–10%) *(71)*
Isoniazid	300 mg p.o. q.d.	Gastrointestinal, hepatitis, peripheral neuropathy
Rifampin	600 mg p.o. q.d.	Gastrointestinal, discoloration of urine, tears, etc.
Rifapentine	600 mg p.o. q.wk	Same as rifampin
Pyrazinamide	25 mg/kg/d	Malaise, gastrointestinal, arthralgia, myalgia
Ethambutol	15–25 mg/kg/d	Optic neuritis, peripheral neuropathy, nausea/vomiting
Ciprofloxacin	750 mg p.o. b.i.d.	Headache, gastrointestinal, rash
Ofloxacin	400 mg p.o. b.i.d.	Headache, gastrointestinal, rash
Streptomycin	15 mg/kg/d i.m.	Deafness, vertigo, renal dysfunction
Amikacin	15 mg/kg/day i.v.	Deafness, vertigo, renal dysfunction
Kanamycin	15 mg/kg/d i.v.	Deafness, vertigo, renal dysfunction
Cycloserine	500 mg p.o. qAM, 250 mg p.o. qPM	Central nervous system, congestive heart failure, rash, hepatitis, tremor
Paraamino-salicylate (PAS) (Paser® granules)	4 g packet mixed in orange juice or apple juice b.i.d.	Gastrointestinal
Capreomycin	1 g i.v. or i.m. q.d.	Deafness, vertigo, renal, dysfunction
Ethionamide	250 mg p.o. qAM, 500 mg p.o. qPM	Central nervous system, Stevens–Johnson, gastrointestinal, SLE syndrome

SLE = systemic lupus erythematosus

inamide, and 6.2% and 1.3% for combined INH and rifampin (MDR) respectively *(32)*. Second, interactions are common between the rifamycins and drugs used to treat HIV infection. Alternative drugs or changes in dosing must be considered when attempting to treat both infections simultaneously. This is because the drugs used to treat TB and HIV have differing effects on the cytochrome P450 (CYP450) system and resulting drug metabolism. Protease inhibitors, for instance, inhibit the CYP450 system and decrease the metabolism of other drugs. The relative effect is ritonavir > amprenavir > indinavir = nelfinavir > sequinavir. Among the nonnucleoside reverse transcriptase inhibitors, delavirdine inhibits CYP450 enzymes, nevirapine induces the enzymes, and efavirenz has both effects. Rifamycins, on the other hand, uniformly induce CYP450 enzymes and increase the metabolism of other drugs. The relative effect is rifampin > rifapentine > rifabutin. Coadministration of rifabutin with ritonavir, saquinavir hard gel capsules (Invirase™), or delavirdine is not recom-

mended. Dosing in other drug combinations must be adjusted. Guidelines published by the CDC should be reviewed for specifics *(32)*.

Some patients receiving therapy for HIV and TB infection at the same time experience a reaction characterized by fevers, lymphadenopathy, worsening chest radiographs (e.g., miliary infiltrates, pleural effusions) or worsening cutaneous lesions or signs of peritonitis. This is termed the "paradoxical reaction" and is thought to be due to reconstitution of the immune system by antiretroviral therapy. In one small series, the reaction occurred in 36% of HIV-infected patients in contrast to only 2% of HIV-seronegative patients *(33)*. Onset of the reaction was 15 ± 11 d after initiating antiretroviral therapy and corresponded with a drop in HIV viral load. The reactions were not associated with changes in cultures or smears from negative to positive, and the patients generally felt well and were not toxic *(32)*.

Directly Observed Therapy

Patient noncompliance with prescribed therapy is of concern because it is a frequent cause of treatment failure and the most common cause for the emergence of drug-resistant TB. In 1991, only 77% of TB patients in the United States completed the prescribed course of antibiotics *(28)*. In 1993, the Advisory Council for the Elimination of Tuberculosis of the CDC recommended that DOT be considered for all patients in areas that do not achieve a 90% completion rate of therapy *(34)*. The World Health Organization currently recommends DOTS (directly observed treatment—short course) for all TB patients worldwide *(35)*. DOT is designed to help the patient take all doses of medications and prevent the emergence of resistance. In DOT, a health care worker watches the patient swallow the medicines. The advantages of DOT are that patients receive their medicines, can be monitored frequently for side effects, and can have all drugs discontinued if they fail to appear for therapy. Erratic self-administration is avoided, and if the patient relapses, the organism will likely remain sensitive to the initial antibiotic regimen *(8)*.

DOT has been successful in improving compliance and decreasing TB case rates. Control of the epidemic of TB in New York City in recent years has been attributed largely to the use of DOT. To conserve on personnel resources, DOT should take advantage of twice- or thrice-weekly dosing regimens *(8)*. Unfortunately, the efficacy of these regimens for drug-resistant TB has not been fully evaluated.

The resolution of cough, fever, and weight loss are important clinical signs of success. The patient's sputum should be cultured on a twice-weekly basis until three consecutive negative sputum cultures have been documented. Conversion should occur within 4 mo if the regimen is going to be successful *(20)*.

TREATMENT OF RESISTANT TB

Current treatment recommendations for TB are to begin patients on a four-drug regimen if the INH resistance rate in the community is ≥4% *(22)*. This recommendation is based on the fact that the majority of MDR-TB cases in the United States are reported from states with INH resistance rates of 4% or more *(36)*. Confusion has arisen because resistance rates in counties or small communities may be unknown or <4% in a given year. Local rates based on small denominators may change rapidly, however, with immigration of resistant cases *(37)*. When determining the risk of INH resistance

in a given population, it may be better to use INH resistance rates based on larger geographical areas or populations.

Drug resistance should be suspected in (1) a patient who has had prior therapy; (2) a patient from an area where drug resistance is prevalent (e.g., Asia, the former Soviet Union, Dominican Republic, etc.); (3) when sputum smears remain positive after 2 mo of therapy; (4) when sputum cultures remain positive after 4 mo of therapy; and (5) when there is unexplained worsening in the patient's chest radiograph or clinical course. Furthermore, a drug should be considered of dubious efficacy if it was the only drug that the bacterium is sensitive to and the drug had been used for more than 1 mo *(38)*.

Drug resistance also may emerge if the antituberculous drugs are poorly absorbed. This may occur in persons who have undergone ileal bypass surgery or gastrectomy, in patients with D-xylose malabsorbtion, and in HIV-infected patients with diarrhea *(39)*. In some cases drug levels at the site of the mycobacterial infection may be far below those of serum. This may occur in patients with thick-walled cavities, areas which are heavily fibrosed, or in areas with extensive calcification *(47)*.

When INH, rifampin, pyrazinamide, and ethambutol or streptomycin cannot be used because of drug resistance, second-line agents must be employed. In general, second-line agents (Table 2) are less desirable than first-line agents because they are more toxic and there is less clinical experience with their efficacy. For instance, the fluoroquinolones ofloxacin and ciprofloxacin have been used successfully to treat TB but the experience is limited *(40)*. In one trial, 9 of 13 patients treated with ofloxacin improved and three were cured when the drug was combined with other second-line agents *(41)*. However, resistance to ofloxacin developed rapidly if the drug was used alone or if it was used with other agents with suboptimal activity.

Among other second-line agents, cycloserine is usually well tolerated, but can have substantial central nervous system (CNS) toxicity. This may be manifested as impaired mentation, psychoses, suicidal ideation, or seizures. Monitoring of serum drug levels may obviate these side effects. Peak serum levels 2 h after a dose should not exceed 25 to 35 μg/mL. The addition of pyridoxine (50–100 mg/d) may be of some benefit *(20)*. PAS is usually well tolerated when given in the form of Paser™ granules (Jacobus Pharmaceutical, Princeton, NJ). In this formulation the drug is adsorbed to methylcellulose beads. The drug is not well absorbed unless it is given in an acid medium such as orange juice, cranberry juice, or applesauce. Patients may be concerned about the appearance of methylcellulose beads in their stools. Ethionamide is the most poorly tolerated antibiotic, especially if it is given with aminosalicylic acid. Gastrointestinal side effects including nausea, vomiting, diarrhea, and a metallic taste are commonly reported. Cross-resistance with INH has been reported *(38)*. This drug should be used only if there are no alternatives *(20)*. The injectable drugs amikacin and kanamycin are valuable adjuncts to any retreatment regimen. Cross-resistance between these agents and streptomycin is rare *(20)*. Their principle toxicities affect the kidney and vestibular and auditory systems. Serum creatinine and drug levels should be monitored carefully as well as monthly audiometry and clinical examinations of vestibular function. There does not appear to be cross-resistance between capreomycin and other injectables, probably because it is a polypeptide antibiotic rather than an aminoglycoside. Capreomycin causes less ototoxicity that the aminoglycosides, but is associated with more nephrotoxicity *(38)*.

Table 3
Suggested regimens for drug-resistant tuberculosis

Resistance	Regimen	Duration
INH + SM	RMP + PZA + EMB	6–9 mo
INH + SM + PZA	RMP + PZA + EMB + AK	6–9 mo
RMP	INH + EMB	18 mo
	+PZA	2 mo
	+SM	Until conversion[a]
INH + EMB + SM	RMP + PZA + FQ + AK or CAP	6–12 mo
INH + RMP + SM	PZA + EMB + FQ + AK	18–24 mo
INH + RMP + EMB + SM	PZA + FQ + AK + two second-line drugs	24 mo after conversion
INH + RMP + PZA + SM	EMB + FQ + AK + two second-line drugs	24 mo after conversion
INH + RMP + PZA + EMB + SM	FQ + AK + three second-line drugs	24 mo after conversion

INH, isoniazid; SM, streptomycin; RMP, rifampin; PZA, pyrazinamide; EMB, ethambutol; FQ, fluoroquinolone such as ciprofloxacin or ofloxacin; AK, amikacin; CAP, capreomycin; second-line drugs include cycloserine, ethionamide, or paraaminosalicylic acid (PAS).

[a] conversion = smears are negative and patient improving.

Data from refs. *20 and 57.*

Recommended regimens for treatment of resistant TB should be based on bacterial susceptibility testing and are listed in Table 3. The following principles should be observed in designing a retreatment regimen:

1. Always seek consultation from an expert when dealing with drug-resistant TB.
2. Radiographic changes are unreliable indicators of relapse or failure. Culture data are necessary.
3. Consider the relative in vitro efficacy of antibiotics against *M. tuberculosis.* Among first-line drugs, rifampin > isoniazid > ethambutol > streptomycin. Among second-line drugs, ethionamide > amikacin > kanamycin = capreomycin > cycloserine = PAS. Among the fluoroquinolones, ofloxacin > ciprofloxacin *(38,42).*
4. Consider results of prior susceptibility tests and susceptibility patterns of strains present in the community.
5. Consider prior treatments. Regard with suspicion any drug that has been used for more than 1 mo in a regimen where it was the only active agent. Such a drug may have diminished activity regardless of in vitro susceptibility testing data *(10).*
6. Retreatment should not be started until reliable data are available from the laboratory.
7. A retreatment regimen should contain at least four drugs and possibly six or seven drugs *(20).* The regimen should include one parenteral drug and three oral drugs. It is important to try to prescribe at least three drugs to which the organism is susceptible *(38).*
8. There is no point in continuing drugs that have failed clinically and/or to which the organism is resistant in vitro.

9. Therapy should always be initiated in the hospital. This allows for monitoring of compliance and side effects.
10. Therapy should begin with a small dose and escalate to a full regimen over 3–10 d.
11. Monitor serum peak and trough levels, as the pharmacokinetics of second-line antituberculous drugs is often unpredictable *(43).* This is especially true in acquired immunodeficiency syndrome (AIDS) patients *(39).*

Some controversy exists about the necessity of including INH for retreatment of mycobacteria reported to be resistant to the antibiotic *(38,44).* Laboratory testing done by the proportionality method labels a bacterium as drug resistant if >1% of the original inoculum grows on agar containing the antibiotic. This means that a large proportion of the bacteria may still be susceptible. Exposure of these bacteria to the antibiotic during treatment might be expected to reduce the population to low enough levels that a cure may be possible. Many experts, however, do not include INH in a treatment regimen if a reputable laboratory has reported resistance.

The success of therapy should be gauged as it is with drug-susceptible TB. Patients should improve clinically and cultures should become negative. Thereafter smear and culture should be obtained every 2 mo for the next 2 yr *(38).* Parenteral agents are usually continued for 6 mo and oral drugs for a total of 18–24 mo after the sputum culture becomes negative *(20).* Drug levels should be followed in patients with AIDS, malabsorption, a history of gastrointestinal surgery, reduced renal function, or if the patient has not improved. Levels are especially important with cycloserine because of the narrow therapeutic-to-toxic margin *(38).*

Traditional indications for surgery in TB have been massive hemoptysis, bronchopleural fistulae, bronchial stenosis, or trapped lung *(45).* Recently the addition of surgery to the management of MDR-TB has increased the cure rate from 65% to >90% *(45).* Patients should be evaluated preoperatively with arterial blood gases and pulmonary function tests, high-resolution computed tomography to define the extent of illness, bronchoscopy to determine if bronchial stenosis is present, and a quantitative ventilation-perfusion scan to determine how much residual lung function will be present after surgery *(46).* Surgery should be postponed until the patient has had at least 3 mo of medical therapy in an attempt to clear the sputum of mycobacteria; however, this may not be possible in up to 50% of patients *(47).* During surgery, an effort is made to remove all grossly damaged lung tissue including infarcted lung and areas with cavities. Scattered nodules may be left behind. Pneumonectomy may achieve a greater cure rate than lobectomy *(47).* The use of muscle flaps or omentum to fill spaces left after lobectomy and to prevent bronchopleural fistulae has been useful, especially if the patient had smear-positive sputum preoperatively. In Pomerantz's series of 130 patients, there was a mortality rate of 2.3% and a complication rate of 12% *(47).* In van Leuven's series of 53 patients, the mortality rate was 1.6% and the morbidity rate was 23% *(48).* Complications in both series included respiratory failure, bronchopleural fistulae, wound problems, postoperative bleeding, recurrent nerve injury, and pneumonia. Long-term antibiotic therapy is still required after surgery to achieve high cure rates *(47).*

PREVENTIVE REGIMENS FOR TB

Persons exposed to, but not actively infected with TB, represent a reservoir of infection. Approximately 10% of these persons may develop active disease within their life-

Table 4
Candidates for Preventive Therapy

Therapy indicated regardless of age:
- HIV-infected persons, or persons with high-risk behaviors (≥5 mm)[a]
- Close contacts of persons with newly diagnosed infectious tuberculosis (≥5 mm)
- Persons who converted their skin test within the past 2 yr (≥10 mm if <35 yr old, and ≥15 mm if ≥35 yr old)
- Persons with chest radiographs showing fibrotic lesions likely to represent old TB (≥5 mm)
- Intravenous drugs users known to be HIV-seronegative (≥10 mm)
- Persons with other immunosuppressive medical conditions (≥10 mm)

Therapy indicated if <35 yr of age and skin test ≥10 mm
- Foreign-born persons from high-prevalence countries
- Medically underserved low-income populations
- Residents of long-term care facilities and health care workers

[a] The criterion for a positive reaction to a skin test (in millimeters of induration) for each group is given in parentheses.

Data from ref. *52*.

times, and if they are HIV infected the risk of active disease approaches 10% per year *(49)*. In the past, persons previously infected with *M. tuberculosis* were thought to be relatively immune to reinfection. It is now known that reinfection can occur, especially if the patient has AIDS *(50)*. In addition, patients receiving treatment for drug-susceptible infection may also become infected with additional organisms resistant to the drugs being used. This is usually seen in severely immunocompromised patients such as those with AIDS, but may occur in other patients as well *(50,51)*.

Persons to be screened for preventive therapy with the tuberculin skin test include those with or at risk for HIV infection, close contacts of persons with active TB, and other persons with medical conditions that make them more susceptible to developing active disease. These include persons with diabetes mellitus, chronic renal failure, leukemia or lymphoma, jejunoileal bypass, gastrectomy, silicosis, or diseases resulting in more than a 10% weight loss *(52)*. The necessity for preventive therapy is based on the person's age, risk group, and skin test reactivity (Table 4).

In most cases, INH is the drug of choice for preventive regimens *(52)*. Generally, 300 mg of the drug is given daily for 6–12 mo. Recently a 2-mo regimen of rifampin (600 mg/d) and pyrazinamide (20 mg/kg/d) was found to be efficacious in HIV-infected patients *(53)*. The CDC recommended this regimen also be considered for patients not infected with HIV *(54)*.

Regimens for the preventive therapy of resistant TB are not well established. INH is probably of little value for persons exposed to INH-resistant TB. Rifampin may be a good alternative. The efficacy of the 2-mo rifampin–pyrazinamide regimen for drug-resistant TB has not been defined. For preventive therapy of persons exposed to MDR-TB, CDC recommends first categorizing patients who have been exposed to persons with MDR-TB according to their risk of developing active disease. Persons at highest risk include those with known HIV infection, persons with risk factors for HIV infection but unknown HIV status, and persons with other conditions known to cause severe

immunosuppression *(55).* Persons in these categories should receive preventive therapy with at least two drugs. A combination of pyrazinamide (25–30 mg/kg/d) and ethambutol (15–25 mg/kg/d), or pyrazinamide and ciprofloxacin (750 mg b.i.d.) or ofloxacin (400 mg b.i.d.) has been recommended. The antibiotics should be given for 12 mo. Two options are recommended for persons not in the above risk groups who have been exposed to MDR-TB. The first option is no preventive therapy. In this instance, the patient should be followed clinically and treated based on the susceptibility of the isolates recovered if they develop disease. The second option is to offer INH or rifampin if the organism is not 100% resistant. Therapy should be given for 6 mo *(55).* In 1994, a group of experts from the American Thoracic Society conferred and recommended a regimen of pyrazinamide (1500 mg/d) and ciprofloxacin (750 mg b.i.d.) for 4 mo for preventive therapy in patients exposed to MDR-TB *(56).* Bacillus Calmette-Guerin may be of value to persons unavoidably exposed to persons with MDR-TB *(38).*

Key Points

- Optimal approaches to the treatment of TB (DOT, use of four drugs initially in communities where INH resistance is ≥4%, follow-up to assess cure) are important to prevention of resistant TB.
- Drug-resistant TB should be managed only in consultation with an expert.
- Choice of drugs for treatment of resistant TB must be guided by susceptibility testing and monitored by follow-up smears and cultures.
- Surgery may play an important role in management of resistant TB.
- Preventive regimens for patients exposed to drug-resistant TB should be guided by susceptibilities of the original organism.

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10
Current Cost-Effective Management of Urinary Tract Infections*

James R. Johnson

INTRODUCTION

New developments in the management of urinary tract infections (UTIs) permit more cost-effective care in the present era of constrained health care budgets, increasing antimicrobial resistance, constantly changing health care delivery systems, and shifts in the traditional physician–patient relationship. The modern physician's challenge is to devise for each patient with UTI a diagnostic and treatment plan that takes into account the individual's clinical syndrome, severity of illness, and underlying host status, and that maximizes efficacy and convenience while keeping costs, toxicity, and induction of antimicrobial resistance to a minimum. Key considerations include empiric short-course therapy with oral trimethoprim–sulfamethoxazole (TMP-SMZ) or a fluoroquinolone for women with acute uncomplicated cystitis; antibiotic and nonantibiotic measures to prevent recurrent UTIs; outpatient oral therapy for patients with mild acute pyelonephritis; prompt conversion to oral therapy and early hospital discharge for patients with more severe acute pyelonephritis; and tolerance of undiagnosed and untreated asymptomatic UTI in low-risk hosts.

This chapter summarizes aspects of contemporary UTI management that are relevant to delivery of maximally cost-effective care, and emphasizes newer developments that represent departures from traditional practice. The presentation is structured around the familiar clinical syndromes of cystitis, pyelonephritis, recurrent UTI, catheter-associated UTI, funguria, and asymptomatic UTI.

CYSTITIS

Clinical Description, Epidemiology, and Etiology

Cystitis connotes infection limited to the urinary bladder. It is a clinical syndrome characterized by irritative voiding symptoms (e.g., dysuria, frequency, and urgency) and bacteriuria/pyuria, in the absence of flank pain or fever to suggest renal or systemic involvement *(1)*. In children too young to report voiding symptoms, cystitis

* All practice suggestions are followed by quality of evidence assessments: [A] supported by randomized trial, meta-analysis, etc.; [B] Supported by weaker empirical evidence; [C] expert opinion.

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may manifest nonspecifically as incontinence, irritability, or a change in the appearance or odor of the urine *(2,3).* Although many patients with what appears clinically to be simple cystitis in fact have occult involvement of the upper urinary tract, since such patients usually respond as well to optimal regimens for cystitis as do patients with infection limited to the bladder the clinical presentation is sufficient to guide management decisions *(4).*

As with all other types of UTI except prostatitis, cystitis is more common among females than males throughout life *(2,3,5,6).* The incidence is greatest among sexually active young women and postmenopausal elderly women. In males, the highest incidence occurs in later life, when prostatic hypertrophy and other chronic medical conditions are increasingly prevalent *(6).* Approximately 80% of cystitis episodes are due to *Escherichia coli,* with the remainder due to *Klebsiella, Proteus,* and rarely other Gram-negative bacilli, plus occasionally enterococci or other Gram-positive species (including, in young women, *Staphylococcus saprophyticus*) *(6–8).*

Pre- and Posttherapy Diagnostic Evaluation

Most otherwise healthy young women with normal urinary tract anatomy and physiology who develop typical symptoms of acute cystitis, in the absence of symptoms suggesting an alternative diagnosis (e.g., vaginitis), do not require a pretherapy urine culture before treatment for cystitis, particularly if urine microscopy or a dipstick test confirms the presence of pyuria [B] *(7–10).* The positive predictive value for bacterial UTI of characteristic voiding symptoms plus pyuria is extremely high in this patient population, such that culture is not needed to confirm the diagnosis *(10).* The distribution of pathogens in acute uncomplicated cystitis, and their susceptibility patterns are highly predictable in the absence of recent antimicrobial use, so identification of the patient's organism and susceptibility testing are not needed to guide therapy *(8,11).* Pretherapy urine cultures add substantially to costs without improving therapeutic outcomes *(12).*

There currently is interest in reducing also the intensity of the nonlaboratory aspects of the pretherapy evaluation for women with suspected cystitis. In some settings, women with UTI symptoms are triaged for evaluation exclusively by a nurse or other physician extender and are managed according to a standing protocol that incorporates the results of the urinalysis (unpublished data). Even more liberal approaches include "over-the-phone" management by a health care professional based strictly on patient-reported symptoms *(13),* and patient-initiated self-diagnosis and antimicrobial treatment *(14,15).* Although none of these approaches has been rigorously compared with conventional management practices, it has been documented that women with a history of recurrent cystitis are highly accurate in identifying when they have a new recurrence *(14,15),* which provides reassurance that neither direct evaluation by a health care professional nor even a urinalysis is essential in every case of acute cystitis in otherwise healthy women. However, there is no published experience with truncated pretherapy evaluations of cystitis in other patient populations, for whom the traditional in-person clinical assessment and urinalysis plus urine culture and susceptibility testing probably are still advisable *(8,16,17).*

Whether follow-up urine cultures are worthwhile in women who are symptom-free after completing therapy for uncomplicated cystitis is questionable [C] *(8,18).* With

today's highly effective treatment regimens such cultures are rarely positive *(11),* and there is no evidence that treating the few patients who do have asymptomatic post-therapy bacteriuria is beneficial. Follow-up cultures may still be advisable in men and in women who have underlying complicating conditions *(16),* although this is unproven [C].

Antimicrobial Therapy (Table 1)

From the many clinical trials that have been done of diverse antimicrobial regimens for acute cystitis in otherwise healthy young women, the following conclusions can be drawn *(11).* First, TMP-SMZ and fluoroquinolone agents historically have given the highest cure rates, with beta lactam agents and fosfomycin trometamol performing comparatively poorly, and nitrofurantoin little studied [A] *(11).* Second, 3 d of therapy with either TMP-SMZ or a fluoroquinolone appears to give the optimal balance of efficacy, adverse effects, and costs, since efficacy is significantly better with 3 d than with single-dose therapy but improves only marginally with longer treatment durations, whereas side effects and drug costs increase with more extended use [A] *(11).* Third, the higher initial drug costs of fluoroquinolones are balanced by cost savings from their slightly higher cure rates and slightly lower rates of adverse effects as compared with TMP-SMZ [B] *(19).* Fourth, to forestall the emergence of resistance to fluoroquinolones, in the absence of contraindications to TMP-SMZ this agent should be the drug of choice for acute uncomplicated cystitis in locales in which antimicrobial resistance to this agent is still infrequent among community-acquired uropathogens [C] *(8,11,19).*

Unfortunately, the prevalence of resistance to TMP-SMZ is increasing globally and in many parts of the United States *(20),* leading to concerns that data from older clinical trials may not reliably predict the current performance of this agent *(11).* Although the impact of TMP-SMZ resistance on response to therapy in acute cystitis remains unknown, fluoroquinolones have been proposed as the agents of choice even for uncomplicated cystitis when the rate of TMP-SMZ resistance among uropathogens in the community exceeds an arbitrary 10–20% threshold [C] *(11).* Trimethoprim–sulfamethoxazole resistance is usually sufficiently prevalent among UTI isolates from patients with underlying urological conditions that oral fluoroquinolones are more suitable for empiric therapy in this context [B] *(7,16,21).* Longer durations of therapy (e.g., 7–14 d) than those used for uncomplicated cystitis in healthy women are usually recommended for cystitis in such patients *(7,16,22,23),* but comparative clinical trial data are lacking [C].

ACUTE PYELONEPHRITIS

Clinical Description, Epidemiology, and Etiology

Pyelonephritis connotes infection of the renal pelvis and/or parenchyma, and is defined clinically by the presence of flank pain and/or tenderness, usually accompanied by fever, in a patient with bacteriuria and pyuria *(7).* Pyelonephritis exhibits many of the same epidemiological associations as cystitis, but is approx 20-fold less common. Patients with pyelonephritis usually feel systemically ill and may have nausea and vomiting, abdominal pain, headache, and myalgias *(1).* Some develop bacteremia, which can precipitate septic shock and its characteristic sequelae.

Table 1
Treatment Regimens for UTI in Adults

Condition	Characteristic Pathogens	Mitigating Circumstances	Recommended Empirical Treatment[a]
Acute cystitis	*Escherichia coli, Staphylococcus saprophyticus, Proteus mirabilis, Klebsiella pneumoniae*	None	3-d oral regimen[b]: TMP-SMZ or trimethoprim (if < 10–20% of *E. coli* resistant), or a fluoroquinolone
		Male, diabetes, symptoms for > 7 d, recent UTI or antimicrobial use, childhood UTI, age > 65 yr	Consider 7–10 d oral regimen[b]: an oral fluoroquinolone, trimethoprim-sulfmethoxazole or trimethoprim (if < 10–20% of *E. coli* resistant), amoxicillin-clavulanate, cefixime, or cefpodoxime proxetil
		Pregnancy	Consider 7-d oral regimen[b]: amoxicillin, macrocrystall line nitrofurantoin, cefixime, cefpodoxime proxetil, or TMP-SMZ (only if <10–20% of *E. coli* are resistant
Acute pyelonephritis	*E. coli, P. mirabilis, K. pneumoniae (S. saprophyticus)*	Mild-to-moderate illness; no nausea or vomiting; no comorbid conditions: outpatient therapy acceptable	Oral[b] fluoroquinolone for 7 d, oral TMP-SMZ for 10–14 d (only if ≤ 5% of *E. coli* resistant), or oral amoxicillin–clavulanate for 14 d (if *Enterococcus* suspected or documented); all with or without an initial parenteral[c] dose of a fluoroquinolone, gentamicin, or ceftriaxone
		Severe illness or possible urosepsis, and/or comorbid conditions: hospitalization required	A parenteral[c] fluoroquinolone, i.v. gentamicin, i.v. ampicillin (or mezlocillin or piperacillin) plus i.v. gentamicin (preferred if *Enterococcus* suspected or documented), i.v. piperacillin–tazobactam, i.v. imipenem, or iv meropenem (if *Enterococcus* suspected or documented and renal function a unstable), or iv ceftriaxone +/− gentamicin, until patient is better; then an oral[b] regimen as for cystitis (or amoxicillin, if only susceptible *Enterococcus*), to complete 14 d therapy

		Pregnancy: hospitalization recommended	Parenteral[c] ceftriaxone, aztreonam, or gentamicin (with or without ampicillin), ampicillin–sulbactam, or piperacillin–tazobactam until patient is better; then oral[b] amoxicillin, amoxicillin–clavulanate, a cephalosporin, or TMP-SMZ (as for cystitis), to complete 14 d of therapy
Complicated UTI (including catheter-associated UTI)	*E. coli, Proteus, Klebsiella, Pseudomonas,* and *Serratia* species; enterococci; staphylococci	Mild-to-moderate illness, no nausea or vomiting: outpatient therapy acceptable	An oral[b] fluoroquinolone (or TMP-SMZ, if organism known to be susceptible) for 10–14 d
		Severe illness or possible urosepsis: hospitalization required	Parenteral therapy[c] as for severe uncomplicated pyelonephritis, with inclusion of activity against *Pseudomonas* (and *Enterococcus,* if Gram stain suggestive or not done), until patient is better; then an oral[b] regimen as for cystitis (or amoxicillin, if if only susceptible *Enterococcus*), to complete 14 d therapy

[a] Treatments listed are those to be prescribed before the etiologic agent is known (Gram staining can be helpful); they can be modified once the agent has been identified. The recommendations are the author's and are limited to drugs currently approved by the Food and Drug Administration, although not all the regimens listed are approved for these indications. Fluoroquinolones (enoxacin, ciprofloxacin, grepafloxacin, levofloxacin, lomefloxacin, norfloxacin, ofloxacin, sparfloxacin, or trovafloxacin) should not be used in pregnancy. Trimethoprim–sulfamethoxazole, although not approved for use in pregnancy, has been widely used. It should be avoided during the first trimester (possible teratogenicity) and near term (kernicterus). Gentamicin should be used with caution in pregnancy because of its possible effects on fetal eighth nerve development. Trimethoprim–sulfamethoxazole should not be used as empiric monotherapy for pyelonephritis in locales where the prevalence of resistance among *E. coli* exceeds 5%.

[b] Multiday oral regimens for adults with normal renal and hepatic function are: TMP-SMZ, 160–800 mg every 12 h; trimethoprim, 100 mg every 12 h; ciprofloxacin, 500 mg every 12 h; grepafloxacin, 400 mg daily; levofloxacin, 500 mg daily; lomafloxacin, 400 mg daily; norfloxacin, 400 mg every 12 h; ofloxacin, 200–300 mg every 12 h; sparfloxacin, 400 mg ×1, then 200 mg daily; amoxicillin–clavulanate, 875 mg every 12 h; amoxicillin, 500 mg every 8 h; cefpodoxime proxetil, 100 mg every 12 h; cefixime, 400 mg daily; and macrocrystalline nitrofurantoin, 100 mg 4× a day.

[c] Parenteral regimens for adults with normal renal and hepatic function are: ciprofloxacin, 200–400 mg every 12 h; levofloxacin, 500 mg daily; ofloxacin, 200–400 mg every 12 h; gentamicin, 5 mg/kg daily; ceftriaxone, 1–2 g daily; aztreonam, 1 g every 8–12 h; ampicillin, mezlocillin, and piperacillin, 1–2 g every 6 h; piperacillin–tazobactam, 3.75 g every 6–8 h; imipenem cilastatin, 250–500 mg every 8 h; and meropenem 500 mg every 8 h.

Adapted, by permission, from Stamm WE, Hooten TM. Management of urinary tract infections in adults. N Engl J Med 1993; 329;1328–1334.

The distribution of pathogens in pyelonephritis is similar to that of cystitis, although the particular strains of *E. coli* that cause pyelonephritis are more likely than cystitis (and particularly than fecal) isolates to express digalactoside-binding adhesins (P fimbriae), hemolysin, and other virulence factors that assist the organism in colonizing the upper urinary tract, foiling host defense mechanisms, and injuring or invading the host *(24).*

Inpatient vs Outpatient, and Intravenous vs Oral Therapy

One of the major recent developments in the management of acute pyelonephritis is the growing acceptance of outpatient therapy with oral agents for stable patients who have mild to moderate severity of illness *(25–29).* Such patients can be observed in the emergency department for a period of time and given intravenous fluid replacement, with or without an initial intravenous dose of antibiotic [A]. If they are clinically stable and able to retain oral fluids, and if they seem likely to comply with an oral regimen and to return for reevaluation in case their condition should worsen or they should develop a complication of therapy, they can then be discharged home to complete a course of oral therapy, with a defined plan in place for follow-up by telephone and/or in person. Those who are more severely ill, clinically unstable, unable to tolerate oral medications, or who have an unstable psychosocial situation should be admitted to the hospital for traditional inpatient therapy *(27,30).* Although outpatient oral management of acute pyelonephritis has been most extensively studied in otherwise healthy young women, it also may be appropriate for certain carefully selected women with underlying medical or urological conditions, children, and men [C].

Empiric Therapy (Table 1)

Although pretherapy urine cultures should be obtained for all patients with acute pyelonephritis [C], culture results are rarely available before therapy must be initiated. Hence, for both inpatients and outpatients the initial therapeutic regimen usually must be selected empirically, with or without the benefit of a urine Gram stain *(8,11,30).* For community-acquired infections in otherwise healthy hosts, *E. coli* is the main pathogen of concern, whereas in nosocomially acquired infections or those occurring in compromised hosts, other more resistant organisms (including *Pseudomonas aeruginosa* and occasionally *Enterococcus*) must be anticipated. Fluoroquinolones, whether given orally or intravenously, are usually suitable for empiric therapy [A] *(11).* Trimethoprim–sulfamethoxazole alone is now inadvisable for empiric therapy even of mild uncomplicated pyelonephritis in many locales because of the risk of therapeutic failure if antimicrobial resistance is present [A] *(11,31).*

For patients treated initially intravenously, many suitable options for empiric therapy exist, including an aminoglycoside with or without added ampicillin; a third-generation cephalosporin or a β-lactam–β-lactamase inhibitor combination agent, either alone or with an aminoglycoside; or a carbapenem or fluroquinolone alone [B] *(8,11,29,30).* Gram-positive cocci in the pretherapy urine Gram stain or a history of urinary tract instrumentation or prior enterococcal UTIs should prompt inclusion of a penicillin with antienterococcal activity or a carbapenem in the initial regimen [C] *(11).*

Conversion to Oral Therapy and Hospital Discharge

Another opportunity for cost savings without sacrifice of therapeutic efficacy is early conversion from intravenous to oral therapy and prompt discharge from the hospital for patients who initially were admitted to the hospital and treated intravenously. Such patients can be switched to oral therapy once their level of symptomatology has improved to below the threshold for hospital admission, even if there is some degree of persisting fever or flank pain [C]. Similarly, inpatients who have converted to oral therapy can be discharged to home once they have demonstrated the ability to take the first dose of the intended oral medication, providing the home situation is suitable. Observation in the hospital for the traditional "extra day" on oral therapy is not cost effective [B] *(32).*

The oral regimen to which hospitalized patients are converted can be selected based on susceptibility test results if these are available by the time the patient is ready for oral therapy. Otherwise, an empiric choice can be made based on the preliminary urine culture results, with a fluoroquinolone used for Gram-negative bacilli and amoxicillin for *Enterococcus* [B] *(11).* The cost savings achievable by converting to oral therapy and possibly shortening the duration of hospitalization far outweigh the greater drug cost of an oral fluoroquinolone as compared with oral TMP-SMZ, which otherwise would be the drug of choice for known susceptible pathogens *(11).* Opportunities for empiric conversion to an oral fluoroquinolone in patients with acute pyelonephritis are sufficiently infrequent that the negative impact of this maneuver on antimicrobial susceptibilities due to increased fluoroquinolone use should be negligible [C].

Diagnostic Evaluations

Patients with acute pyelonephritis often are sufficiently ill that it is reasonable to check serum chemistries and blood counts before and possibly again during therapy [C]. Pretherapy blood cultures, although commonly done, rarely contribute meaningfully to patient management *(33).* Urinary tract imaging studies and urological consultation can be reserved for patients with pyelonephritis who on the basis of the history or physical examination are suspected at the outset of having an underlying urological abnormality or an anatomical complication of infection in need of instrumentation, and for patients who fail to respond appropriately to medical therapy [C] *(7,18,34).* Lingering symptoms or fever despite several days of therapy are not indications for imaging studies providing the overall clinical trend is favorable *(34),* whereas absence of clear improvement after 48 h of appropriate medical therapy is worrisome and should prompt further evaluation [C] *(35–37).*

Because of its greater sensitivity, computed tomography (CT) is the most cost-effective imaging modality for suspected intrarenal and perinephric abscesses and emphysematous pyelonephritis [C] *(37–39).* For optimal performance renal CT should be done with intravenous contrast enhancement *(39)* and, for maximal economy, without an initial sonogram. Ultrasonography is useful mainly if the goal is to evaluate for hydronephrosis or for following abnormalities detected on an initial CT (if visible sonographically) [C] *(29,37,40).* Spiral CT, if available, is a superior imaging modality specifically for upper urinary tract stones [C] *(39).*

Duration of Therapy

The duration of therapy for acute pyelonephritis must be individualized for each patient *(8,11,41–43).* For women with moderate to severe illness who are initially hospitalized and given an aminoglycoside-containing intravenous regimen followed by oral therapy with ampicillin or TMP-SMZ, 14 d of total therapy is highly effective [A] *(44).* For otherwise healthy women treated as outpatients for mild to moderately severe pyelonephritis, 1 wk of oral ciprofloxacin is as effective as 2 wk of oral TMP-SMZ, and is less likely to encounter antimicrobial resistance [A] *(31).* For women with underlying complicating conditions and for men, 14 d of total therapy for pyelonephritis is a reasonable target, which can be adjusted up or down based on initial severity of illness and rapidity of response to therapy [C] *(7,30).*

RECURRENT UTI

Clinical Description, Epidemiology, and Etiology

Recurrent UTI, commonly defined as more than two to three acute UTI episodes per year, is experienced by up to 20% of urologically normal healthy young women *(45,46),* and also is common among patients with predisposing urological abnormalities (e.g., as discussed below for catheter-associated UTI). Risk factors for recurrent UTI other than anatomical and functional abnormalities of the urinary tract include female gender, sexual intercourse (particularly with the use of spermicide-based contraception), and (for women) being postmenopausal or a nonsecretor of blood group substances *(45,46).* In adult women, the spectrum of pathogens causing uncomplicated recurrent UTI is the same as that causing first episode cystitis.

Prevention

Women who have frequent UTIs rarely have a correctable underlying anatomical or urological abnormality, and should not be investigated for these unless they have infections that are difficult to eradicate, severe infections, or repeated early relapses caused by the same bacterial strain [B] *(45).* Instead, several noninvasive preventive measures can be tried. Women who use spermicide-based contraception can switch to an alternative method, to avoid the vaginal overgrowth with *E. coli* that accompanies vaginal spermicide use and predisposes to UTI [C] *(45,47).* Postmenopausal women can use topical (and probably systemic) estrogen replacement therapy to restore a premenopausal lactobacillus-dominated vaginal flora instead of the *E. coli*-dominated flora that often accompanies the hypoestrogenic postmenopausal state [B] *(47,48).* Antimicrobial prophylaxis, whether taken daily, several times weekly, or postcoitally (when UTIs are associated with coitus), is highly effective in reducing the frequency of symptomatic UTI episodes in young women with recurrent UTIs, and may be effective also in functionally intact elderly women [A] *(45,49).* Alternatively, women with recurrent UTI can be given a supply of antibiotics to self-administer when they first develop characteristic symptoms of UTI [A] *(14,15).* Although this approach costs approximately the same as continuous antimicrobial prophylaxis, it entails less total antibiotic use *(15),* and may be preferred by women who have infrequent or mild noncoitus-associated UTI recurrences, or who wish limit their intake of antibiotics.

CATHETER-ASSOCIATED UTI

Clinical Description, Epidemiology, and Etiology

The term "catheter-associated UTI" is commonly applied to any UTI that develops in a patient who has an indwelling bladder catheter in place, whether or not the infection is accompanied by local or systemic symptoms or signs *(50).* Catheter-associated UTI is the most common form of nosocomial infection in acute care hospitals, and is almost universally present among patients with chronic indwelling catheters in the community and in long-term care facilities *(50).* Predisposing factors include the presence of the catheter itself, female gender, duration of catheter use, violations of the closed catheter drainage system or of other principles of appropriate catheter care, and (in the acute care setting) absence of antimicrobial therapy *(50).* Causative organisms are divided between Gram-negative bacilli (among which non-*E. coli* species, including *Pseudomonas aeruginosa* and *Providencia stuartii,* are much more prominent than in uncomplicated UTI), Gram-positive cocci (including coagulase-negative staphylococci), and yeasts, particularly in patients receiving antimicrobial agents *(50).*

Prevention

Avoidance of indwelling catheter use and proper nursing care of the catheter system (e.g., avoidance of breaks between the catheter and the drainage tubing) are the only two currently recommendable interventions for preventing catheter-associated UTI [A] *(50).* Prophylactic systemic antibiotic therapy, while protective in the short term, selects for resistant organisms, hence on balance is probably more harmful than helpful [C] *(50).*

Treatment

The most important guiding principle for the treatment of catheter-associated UTI is that the great majority of episodes do not require treatment at all [C] *(50).* Therapy should be given only when UTI in a catheterized patient is accompanied by local irritative symptoms or by constitutional signs or symptoms for which there is no other explanation (and not merely pyuria, which is almost universal among bacteriuric catheterized patients regardless of the presence or absence of symptoms). A corollary is that in the absence of such clinical indicators the urine of a catheterized patient should not be tested for infection [C]. Adherence to this principle could avoid countless unnecessary urinalyses and urine cultures and much needless antibiotic use. A possible exception to this rule involves asymptomatic catheter-associated UTI that is discovered at the time of catheter removal from acutely catheterized patients *(51).* Because approximately 25% of such patients go on to develop symptomatic UTI if not given antimicrobial therapy, preemptive short-course treatment may be warranted [B] *(51).*

When catheter-associated UTI must be treated, treatment can be as for complicated cystitis or pyelonephritis (Table 1), depending on the severity of illness. Oral TMP-SMZ (if the organism is known to be susceptible) or a fluoroquinolone can be used for Gram-negative bacilli, and amoxicillin for susceptible Gram-positive cocci, in patients with absent or only mild constitutional symptoms [C]. More severely ill patients generally require parenteral therapy. For patients who have lower urinary tract symptoms only, it is reasonable to limit treatment to ≤7 d, whereas febrile patients or those with

constitutional symptoms may warrant treatment as for pyelonephritis [C]. For symptomatic infected patients who need continued catheter drainage, catheter exchange during antimicrobial therapy increases the likelihood of cure [B] *(52).*

FUNGAL UTI

Clinical Description, Epidemiology, and Etiology

Fungal UTI, an increasingly frequent problem, is generally limited to hosts with an obvious predisposing factor such as diabetes mellitus, antibiotic therapy, and/or indwelling bladder catheter use *(53). Candida* species predominate overwhelmingly as the causative agents, with *Aspergillus* and other fungi only rarely causing UTI, and then only in profoundly immunocompromised hosts.

Treatment

The great majority of fungal UTIs are asymptomatic and, like catheter-associated UTI (which many fungal UTIs are), require no specific diagnostic testing or antifungal therapy [B] *(53–57).* Although the morbidity and mortality associated with funguria are considerable, this is due primarily to the comorbid conditions that are commonly present in patients who develop funguria *(53,54).* Complications attributable to fungal UTI *per se* are rare *(53,58).* When treatment is judged to be necessary because of clinical manifestations of infection, fluconazole is usually the treatment of choice [A] *(53,59–61).* It should be given orally in patients able to tolerate and absorb oral medications [C]. Bladder washout with amphotericin B cannot be recommended, as it is more cumbersome and noxious than fluconazole, may be less effective even for infections limited to the bladder *(57,60–62),* and would be expected to fail when the infection is tissue invasive, involves the upper urinary tract, or has spread (or initially originated) outside of the urinary tract. The latter possibility is important to consider in critically ill patients with funguria, in whom funguria may be a harbinger of incipient or established disseminated candidiasis [B] *(53,63–65).* Although routine preemptive antifungal therapy for critically ill surgical patients with funguria has been advocated *(65),* whether this approach truly improves outcomes remains to be definitively determined [C].

ASYMPTOMATIC BACTERIURIA

Clinical Description, Epidemiology, and Etiology

Asymptomatic bacteriuria (ABU) is defined by the presence of bacteria in the urine in a patient who does not have any symptoms (or, more generally, any clinical manifestations whatsoever) attributable to the bacteriuria, irrespective of the presence or absence of pyuria *(1).* At any point in time, ABU is present in a fraction of the healthy population, including males and females of all ages. However, the likelihood of ABU is greatest throughout life in females, and increases in both genders with advancing age and progressive debility *(66).* The spectrum of organisms causing ABU is generally similar to that of symptomatic UTI, with polymicrobial infection and certain bacterial species (e.g., enterococci, coagulase-negative staphylococci, and Gram-negative bacilli such as *Providencia*) encountered more frequently *(66).*

Treatment

Treatment of ABU has been recommended for patients in whom ABU is a known or strongly suspected direct contributor to adverse outcomes [A] *(9,67).* Such patients include infants, pregnant women, patients about to undergo urinary tract instrumentation, recent renal transplant recipients, neutropenic patients, and individuals with postcatheterization bacteriuria. In most other patients, as ABU is of no known clinical significance, its treatment is without defined benefit but predictably will result in increased costs, toxicity, and antimicrobial resistance [B] *(7,23,66,67).* Consequently, except for in the above patient groups urine from asymptomatic patients generally should not be tested to detect ABU, and if for some reason UTI is documented in a patient without signs or symptoms attributable to the infection treatment usually should be withheld [B].

SUMMARY

By using only the most helpful diagnostic tests, selecting the least expensive and least toxic antimicrobial regimens from among the most effective alternatives, and providing a sufficient but not excessive treatment duration in an appropriate setting, physicians can limit costs and improve clinical outcomes for patients with UTI while reducing selective pressure for antimicrobial resistance. Several departures from traditional UTI management practices are now known to be safe and cost effective, and hence can be recommended for standard use.

KEY POINTS

- Practitioners must devise for each patient with a UTI a diagnostic and treatment plan that takes into account the individual's clinical syndrome, severity of illness, and underlying host status, and that maximizes efficacy and convenience while keeping costs, toxicity, and induction of antimicrobial resistance to a minimum.
- Although empiric short course therapy with oral trimethoprim–sulfamethoxazole is appropriate for women with acute uncomplicated cystitis, when the rate of trimethoprim–sulfamethoxazole resistance among uropathogens in the community exceeds 10–20% oral fluoroquinolones are more suitable for empiric therapy.
- Women who have frequent UTIs rarely have a correctable underlying anatomical or urological abnormality, and should not be investigated for these unless they have infections that are difficult to eradicate, severe infections, or repeated early relapses caused by the same bacterial strain.

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11
Sexually Transmitted Diseases

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INTRODUCTION

Sexually transmitted diseases (STDs) are a complex set of syndromes involving more than 25 pathogens acquired through sexual activity. A majority of the 12 million Americans infected with STDs each year are not treated in a public STD clinic *(1).* This emphasizes the need for *all* clinicians to be aware of and provide management for STDs according to the Center for Disease Controls' (CDC) STD Treatment Guidelines *(2).* In an era of emerging antimicrobial resistance and incurable viral STDs, prevention of infection is crucial.

Many STDs are asymptomatic. Undetected, the infections can eventually result in serious complications. Unfortunately, the frequently long interval between initial infection and sequelae such as infertility or cancer contributes to a lack of public awareness regarding the impact of STDs *(1).* The gravest consequence of STDs is the increased risk of acquiring human immunodeficiency virus (HIV). Both ulcerative STDs (chancroid, syphilis, and genital herpes) and inflammatory STDs (gonorrhea, *Chlamydia* infection, and trichomoniasis) increase the risk of HIV acquisition *(1,3).*

Management of STDs is often complex because of the need to deal with more than one patient (index patient and partner). The clinician who neglects the "partner" misses an opportunity to prevent further transmission of disease and increases the risk that the index patient will be reexposed. A coordinated approach to treat both patient and partner is needed to effectively respond to the STD epidemic.

Risk assessment (including sexual history) and clinical evaluation are essential components of effective STD management *(4).* The sexual history should include questions regarding sexual contact with men, women, or both. Ascertaining the mode of sexual practices (oral, anal, vaginal) is helpful because certain STDs, including HIV, are transmitted more efficiently by anal or vaginal intercourse. Evaluation should include questions on specific exposures such as a new partner, a partner experiencing discharge, or personal/partner use of intravenous drugs *(4).* STD practice guidelines also advise obtaining history of serologic testing for syphilis and HIV as well as inquiries about hepatitis B vaccination *(4).* Knowledge of previous antibiotic use is important because use of antibiotics may mask symptoms of STDs or affect resistance patterns of the infecting organism. Travel history and demographic information provide clues to the likelihood of certain STDs.

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Clinical evaluation should also include a review of systems, targeting the genitourinary tract *(4)*. A focused physical examination can then be used to investigate any complaints suggestive of an STD. The information obtained through risk assessment and clinical evaluation should direct appropriate confirmatory diagnostic testing (symptomatic patient) or screening (asymptomatic patient). Rapid tests such as wet mount of vaginal discharge or Gram stain of urethral discharge may aid in starting presumptive therapy (syndromic treatment) *(5)*.

STD management goals include microbiologic cure, alleviation of signs and symptoms, prevention of sequelae, and prevention of transmission *(2)*. In most settings, instituting treatment for a symptomatic patient based on symptoms (presumptive diagnosis) is appropriate *(5)*. The remainder of case management is preventive and involves: (1) contact (partner) notification and treatment; (2) counseling on risk reduction; (3) condom promotion; and (4) efforts to facilitate treatment compliance *(5)*, including use of directly observed therapy single session (DOT-SS) when possible.

Screening of partners and asymptomatic patients is an important component of STD management. Currently, the standard approach for handling partners is for the clinician to personally screen and treat partners *(5)*. The Advisory Committee for HIV and STD Prevention (ACHSP) has made the following recommendations regarding screening *(6)*:

- All sexually active women under the age of 25 yr who visit a health care provider for any reason should be screened for *Chlamydia* and gonorrhea at least once per year.
- Routine screening of sexually active young men for *Chlamydia* and gonorrhea should be implemented in settings or for subpopulations in which the prevalence is >2%.
- Older individuals in "high-risk" groups of either gender should be screened yearly for *Chlamydia* and gonorrhea: substance abusers, persons with history of STDs, those with more than one sex partner per year, those in correctional facilities, and persons from communities with high rates of STDs.
- Serologic screening for syphilis should be conducted in high-risk persons (those with multiple sex partners, who exchange sex for money or drugs, are incarcerated, or use illicit drugs).
- Persons already infected with HIV should be screened routinely for STDs.

DISEASES CHARACTERIZED BY GENITAL ULCERS

Genital lesions can be divided into ulcerative and nonulcerative lesions. In most parts of the United States, syphilis and genital herpes are the usual causes of ulcerative lesions *(2)*. In developing countries, the differential broadens to include chancroid, donovonosis, and lymphogranuloma venereum (LGV). Other causes of ulcerative lesions that should be considered are trauma, malignancy, fixed drug eruption, and Behçet's and Reiter's syndromes. Multiple studies have shown that genital ulcer disease (GUD) is a risk factor for the acquisition of HIV infection *(3)*.

In practice, it is often difficult to differentiate among the GUDs *(7)*. The clinician will usually need to treat the most likely cause of GUD while awaiting the results of diagnostic tests. Essential components to the evaluation of patients with GUD include a dark-field examination or direct immunofluorescence test (DFA) for *Treponema pallidum,* a culture or antigen test for herpes simplex virus (HSV), and a culture for *Haemophilis ducreyi.* Even after diagnostic evaluation, 25% of patients with GUD will not have a laboratory-confirmed diagnosis *(2)*. A multiplex polymerase chain reaction

(PCR) with a sensitivity that exceeds 95% will soon be commercially available for the diagnosis of *H. ducreyi,* HSV, and *T. pallidum (8).*

Chancroid

The classic triad of chancroid is an undermined, painful, purulent ulcer with ragged edges; however, clinical diagnosis is unreliable and insensitive *(7).* After an incubation period of 4–7 d, the initial lesion appears. It is a tender erythematous papule that becomes a pustule and eventually erodes into an ulcer. Painful inguinal adenitis is present in 40% of patients *(9).* Chancroid is the most common GUD in many developing countries. Although not common in the United States, outbreaks have occurred in major cities of industrialized countries *(7,9).* Risk factors associated with chancroid acquisition appear to be related to low socioeconomic status, geographic origin, commercial sex, and lack of circumcision *(10).* The incidence of chancroid is higher in military personnel, tourists, and drug users *(9).* During epidemics, prostitutes have been the usual reservoir. Sexual contact is the only mode of acquisition and there is no asymptomatic reservoir *(9). Haemophilus ducreyi,* the etiologic agent of chancroid, is a Gram-negative facultative anaerobic bacillus that requires breaks in the epidermis or trauma to establish disease *(9).* A definitive diagnosis of chancroid requires identification of *H. ducreyi* from specimens inoculated onto culture media. A probable diagnosis can be made if the patient has one or more painful genital ulcers, no evidence of *T. pallidum* (dark-field or by serologic testing), a clinical presentation typical for chancroid, and negative HSV testing *(2).* The recommended treatment regimens for chancroid are summarized in Table 1 *(2).*

Treatment failures and development of resistance have been reported for chancroid. Decreased response to therapy has been noted in persons who are HIV seropostive and in uncircumcised men *(11).* Therefore, all patients with chancroid should be tested for HIV. Patients with conditions predisposing to treatment failure should be monitored closely; they may need more intensive therapy and may not respond as predictably to single-dose therapy *(2).*

Development of resistant *H. ducreyi* is a concern. Plasmid-mediated antimicrobial resistance has been described for ampicillin, sulfonamides, chloramphenicol, tetracycline, streptomycin, and kanamycin *(9).* Ceftriaxone is acceptable therapy for chancroid in the United States. However, one study in Kenya showed a reduced cure rate using ceftriaxone (73%) *(12).* The macrolides and quinolones all have excellent in vitro activity against *H. ducreyi (13).* A strain of *H. ducreyi* in Thailand that had intermittent susceptibility to ciprofloxacin has been reported, suggesting that surveillance for development of quinolone-resistant strains is warranted *(13).* Owing to high failure rates and increasing resistance, neither trimethoprim–sulfamethoxazole nor amoxicillin–clavulanic acid should no longer be used for the treatment of chancroid (*11,13).*

Herpes Simplex Virus

Manifestations of HSV infection are variable and many persons have mild or unrecognized symptoms *(14).* Primary genital herpes infection occurs in HSV seronegative individuals (never had either type of HSV). Nonprimary first episode of genital herpes infections occur in patients who have had previous HSV-1 and now have an HSV-2 genital infection *(14).*

Table 1
Treatment of Chancroid

Treatment	Duration
Azithromycin, 1 g orally	Single dose
Ceftriaxone, 250 mg intramuscularly (i.m.)	Single dose
Ciprofloxacin, 500 mg orally twice a day	3 d
Erythromycin base, 500 mg orally 4 × a day	7 d

Primary genital infections are more likely to be characterized by constitutional symptoms (fever, headache, and myalgias) and prominent localized symptoms (pain, dysuria, and tender inguinal adenopathy). Lesions begin as bilateral papules or vesicles that coalesce into areas of ulcerations *(14).* Symptoms usually last 12–20 d and viral shedding occurs for about 12 d *(14).* Complications associated with primary genital herpes can include aseptic meningitis, transverse myelitis, urinary retention, monarticular arthritis, hepatitis, thrombocytopenia, and extragenital lesions. Cervical involvement (cervicitis and asymptomatic shedding) is common with HSV. Although bacterial superinfection is uncommon, yeast vaginitis is frequently encountered in initial HSV infection *(14).* HSV proctitis, the most common cause of nongonococcal proctitis in men, is another clinical manifestation of HSV *(14).*

Recurrent genital herpes infections cause more localized symptoms and have a shorter duration of lesions (9–11 d) and viral shedding (up to 4 d) than initial episodes *(14).* Approximately 90% of patients with primary HSV-2 infection and 60% of patients with primary genital HSV-1 develop recurrence within the first 12 mo of infection *(14,15).*

Genital herpes is the most common cause of GUD in the United States *(16).* It is estimated that one out of four women and one out of five men will become infected with HSV during their lifetimes *(1).* The presence of HSV-2 antibody is related to the lifetime number of sexual partners, age at first sexual encounter, and history of other STDs. There is a higher rate of HSV-2 antibody among African Americans and in those of lower socioeconomic status *(14,17).* Transmission of HSV occurs through intimate contact with a person shedding virus in mucosal, genital, or oral secretions *(14).* Most cases of genital HSV are acquired from asymptomatic persons *(18).* All episodes of HSV (including asymptomatic cases) render a person infectious *(14).*

Although HSV-1 has been historically associated with nongenital lesions, *both* HSV types can cause genital lesions *(14).* The diagnosis of genital HSV can be difficult, as patients and partners may be asymptomatic. Only 60–70% of patients will have the classical presentation of painful vesicles *(18).* Routine viral culture with typing is recommended so as to counsel patients regarding the frequency of recurrences *(15,18).* Viral culture is only 50% sensitive and therefore failure to isolate HSV does not rule out HSV infection *(14).* HSV DNA detection by PCR and HSV antigen detection by EIA or FA are useful assays *(14).* The serologic testing that is currently available is not specific and is not routinely recommended.

The management of genital herpes must include counseling regarding the natural history and transmission of HSV *(18).* Patients should be counseled that they may have

acquired infection recently or months or years earlier (and were asymptomatic until their current episode). During the initial visit, management should be directed toward palliation of symptoms, as patients may be too concerned with physical illness to appreciate the implications of a chronic viral STD. A return visit to discuss long-term issues may be beneficial and can provide time to discuss methods to reduce transmission (use of condoms at all times and abstinence during recognizable prodrome or recurrences) *(18).*

Pharmacotherapy is an important part of management of genital herpes and focuses on the use of three nucleoside analogs: acyclovir, valacyclovir, and famciclovir. All three drugs have been shown to reduce the duration and severity of primary and recurrent attacks of genital herpes *(18)* (*see* Table 2). Topical acyclovir is not recommended, as it is less effective than oral acyclovir *(2).* Antiviral therapy is recommended for all patients with clinical first-episode genital HSV *(18).*

There are two basic strategies for treatment of recurrent genital herpes: episodic therapy and suppressive therapy. Episodic therapy involves treating individual episodes when they occur; treatment can be patient initiated with the onset of symptoms. Daily suppressive therapy is used to prevent frequent recurrences. Patients with frequent recurrences (≥6 episodes per year), severe physical or emotional distress, and potential for transmission to sexual partners may benefit from suppressive therapy *(2).* Although breakthrough episodes may occur on suppressive therapy, all three drugs provide suppression of recurrences and may reduce recurrences by 75% *(2).* Daily treatment with oral acyclovir reduces but does not eliminate subclinal shedding of HSV-2 *(14).* Periodically, suppressive therapy should be discontinued to determine if it is still needed *(14,19).*

Baseline in vitro resistance of HSV for acyclovir is ~3% and long-term suppression in immunocompetent hosts does not appear to select resistant virus *(19).* Typically, acyclovir-resistant HSV infection in the immunocompent patient is not associated with clinical failure, although rare cases have been reported *(19,20).* Most acyclovir-resistant HSV infections occur in immunocompromised hosts. Development of resistance to acyclovir occurs at the rate-limiting step of the enzyme thymidine kinase (TK). Mechanisms of resistance to acyclovir are TK deficiency (most common) and alterations in TK or DNA polymerase *(14,21).* Most acyclovir-resistant strains are resistant to famciclovir and valciclovir, as both have mechanisms of action similar to that of acyclovir *(14).* Susceptibility testing for HSV isolates is not routinely recommended. However, if lesions persist in a patient receiving acyclovir, resistance of the HSV strain should be suspected and susceptibility testing should be considered *(18).* Most acyclovir-resistant HSV infections require alternative agents including foscarnet, cidofovir, and trifluridine.

Foscarnet, a viral DNA polymerase inhibitor, has been used topically and parenterally in patients with acyclovir-resistant HSV infection *(20,21).* Foscarnet infusion resulted in a clinical response of 81% of 26 patients with acyclovir-resistant HSV infection *(21).* Success with topical 1% foscarnet cream has been reported in an immunocompent host *(20).* Despite the toxicity of foscarnet (including nephrotoxicity, electrolyte imbalance, and anemia), it is the preferred agent for acyclovir-resistant HSV infection *(14,18).* HSV infections that occur after foscarnet therapy may be acyclovir susceptible or acyclovir resistant *(21).* Foscarnet-resistant HSV may emerge in the setting of prolonged foscarnet use *(14).*

Table 2
Treatment of HSV Infections

Indication	Drug	Dose	Duration	Comments
First episode of genital herpes	Acyclovir	200 mg p.o. 5×/d	10–14 d	If not healed after 2 wk of therapy, treat for an additional 7 d.
	Acyclovir	400 mg p.o. 3×/d		
	Valacyclovir	1000 mg p.o. 2×/d		
	Famciclovir	250 mg p.o. 3×/d		
First episode of herpes proctitis	Acyclovir	400 mg p.o. 5×/d	10–14 days	
Recurrent genital herpes	Acyclovir	400 mg p.o. 3×/d	5 days	Therapy shortens episode by 1–2 d.
	Acyclovir	200 mg p.o. 5×/d		
	Valacyclovir	500 mg p.o. 2×/d		
	Famciclovir	125 mg p.o. 2×/d		
Suppressive therapy	Acyclovir	400 mg p.o. 2×/d		A 500-mg dose of valacyclovir may be less effective in patients who have very frequent recurrences (≥10 episodes per year).
	Valacyclovir	250 mg p.o. 2×/d		
	Valacyclovir (see Comments)	500 mg p.o. 1×/d		
	Valacyclovir	1000 mg p.o. 1×/d		
	Famciclovir	250 mg p.o. 2×/d		
Asceptic meningitis/disseminated	Acyclovir, intravenous	5 mg/kg q8h		After clinical improvement, oral valacyclovir can be given for a total of 10–14 d.
Acyclovir-resistant	Foscarnet, intravenous	40mg/kg q 8h	Until clinical resolution	
	Cidovovir	1% Topically	5 d	

Data from refs. *2,14.*

Topical cidofovir, a nucleotide analog, has been successfully used in immunocompromised patients with acyclovir-resistant HSV infections *(22).* In a trial of cidofovir gel, 10 of 20 AIDS patients had reduction in lesions by at least 50%, compared to no healing by placebo *(22).* Because of renal toxicity with intravenous cidofovir, topical cidofovir is preferred for treatment of genital herpes. Trifluridine, a nucleoside analog, is used frequently for the treatment of ophthalmic HSV infections. A series of 26 patients with HIV who had mucucutaneous HSV infections unresponsive to acyclovir demonstrated complete healing in 7 and partial healing in 14 patients using trifluridine *(23).*

Immunocompromised patients may have prolonged and severe recurrent genital herpes. Dissemination requires treatment with 5–10 mg/kg of acyclovir intravenously (*see* Table 2). HSV is a common clinical presentation of HIV infection and most HSV-infected persons with HIV will respond to acyclovir *(18).* Most patients with HIV and HSV infection will benefit from chronic suppressive therapy *(14).* As mentioned previously, acyclovir resistance is rare but is more common in the immunocompromised host.

Pregnant women with genital HSV may transmit the virus to their babies. The risk of transmission of neonatal herpes from an infected mother is higher (50%) for women who have acquired primary HSV infection near the time of delivery than for those mothers with new HSV-2 but previous HSV-1 infection (20%) *(2,14).* The lowest risk of transmission to the neonate is from mothers with recurrent herpes or HSV acquired during the first half of pregnancy (3%) *(2).* Therefore, prevention of neonatal herpes should focus on prevention of acquisition of genital HSV infection during late pregnancy. Susceptible women (HSV-2 or HSV-1 seronegative with seropositive partners) should be counseled to avoid unprotected genital and oral sexual contact during late pregnancy. At the onset of labor, all women should be examined and questioned regarding genital herpes and those with no clinical evidence of lesions can be delivered vaginally *(2).* Although routine treatment of recurrent HSV in pregnant women is not currently recommended, the first clinical episode of genital herpes during pregnancy may be treated with oral acyclovir *(2).*

Syphilis

Syphilis is a systemic infection with periods of active clinical disease and periods of latency. The primary stage develops approx 3 wk from exposure and is characterized by a chancre (painless lesion) and bilateral nontender regional adenopathy *(24).* The ulcerative lesion with well-circumscribed borders can be found at genital, perirectal, perianal, or nongenital sites *(24).* Untreated, the chancre heals in a few weeks. Secondary syphilis represents multiplication and dissemination of treponemes throughout the body. Occurring up to 6 mo after the initial chancre, this stage is characterized by low-grade fever, malaise, sore throat, headache, adenopathy, and cutaneous or mucosal rash. Mucous patches in the oral cavity or genital tract, alopecia, hepatitis, or rarely nephrotic syndrome may develop *(24).*

Persons with no clinical syndrome but positive serologic tests are said to have latent syphilis. Early latency occurs during the first year of infection and late latency occurs more than 1 yr from initial chancre. In 25% of untreated syphilis cases, latency can be interrupted by a second clinical relapse or recrudescence *(24).* Tertiary (late) syphilis

develops in one-third of untreated patients 10–25 yr after the initial infection *(25).* Treponemes invade the central nervous system (CNS), cardiovascular system, eyes, skin, and other internal organs. Gummas, which are locally, destructive lesions involving the liver, skin, bones, and other organs, can develop *(24).* Transmission of syphilis to sexual contacts does not occur during this stage; however, sexual partners and infants born to mothers with any stage of syphilis should be evaluated according to the Centers for Disease Control (CDC) guidelines *(2).*

The incidence of syphilis in the United States has fluctuated, with peak rates occurring recently during the late 1980s. Syphilis incidence is currently at its lowest since 1941, 2.6 per 100,000 population in 1999 *(26).* Syphilis remains more common in non-Hispanic blacks and is concentrated in the southern United States *(26).* Historically, syphilis has been associated with the use of illicit drugs (particularly crack cocaine) and exchange of sex for drugs *(24,26,27).*

It is well recognized that syphilis facilitates transmission of HIV, and all patients with syphilis should be tested for HIV infection *(2,3).* Nearly all cases of syphilis are acquired by direct sexual contact with lesions from an individual with primary or secondary syphilis. However, syphilis can be transmitted congenitally and less commonly by the bloodborne route (blood transfusion/needle sharing), nonsexual personal contact, and accidental direct inoculation *(25).*

Treponema pallidum, the etiologic agent of syphilis, is a spirochete that can be visualized by dark-field microscopy and silver staining *(25).* Dark-field examination or DFA tests of lesions or tissue are the methods used to make a definitive diagnosis of syphilis *(2).* A presumptive diagnosis can be made using two types of serologic tests: the nontreponemal, which includes the VDRL (Venereal Disease Research Laboratory) and the RPR (rapid plasma reagin), and treponemal, which includes the FTA-ABS (fluorescent treponemal antibody absorption) and the MHA-TP (microhemagglutination assay for *T. pallidum* antibody) *(27).* Positive nontreponemal tests require confirmation with treponemal antibody tests. The nontreponemal tests are sensitive but not specific (~70% sensitive in primary and late disease and 99% sensitive in secondary) *(25).* Therefore, a negative test result does not exclude the diagnosis of early syphilis.

False positive nontreponemal tests for syphilis are common in individuals with autoimmune diseases, viral infections (particularly Epstein–Barr and hepatitis viruses), protozoal infections, and mycoplasmal infections, as well as in the elderly, pregnant women, and intravenous drug users *(27).* About 1–2% of patients with secondary syphilis will exhibit a prozone reaction (excess anticardiolipin antibody present in undiluted serum) which results in a false-negative result with RPR testing *(27).*

The nontreponemal tests are quantitative and correlate well with disease activity. Sequential serologic tests should be performed by the same testing method (VDRL or RPR) and in the same laboratory if possible. Failure of a nontreponemal titer to decrease fourfold (two dilutions, e.g., from 1:16 to 1:4) within 6 mo after therapy for primary or secondary syphilis identifies persons at risk for treatment failure *(2).* It is expected that a nontreponemal test will become nonreactive; however, some patients are serofast and their nontreponemal antibodies persist at a low titer for the remainder of their lives *(2).* Treponemal tests often remain reactive for the remainder of life regardless of disease activity and should not be used to assess clinical response *(2).* The

new multiplex PCR should be commercially available soon and appears to be more sensitive for the detection of *T. pallidum* than dark-field microscopy (91% vs 81%) *(8).*

Penicillin G is the drug of choice for treatment of patients with all stages of syphilis (Table 3) *(2).* Second-line therapies include tetracycline or erthromycin *(2).* Although penicillin treatment for syphilis is the standard of care, no adequately conducted comparative trials have been performed and even less data are available regarding nonpenicillin regimens. Ceftriaxone has been used but the optimal dose and duration of therapy is not established and most agree that single-dose ceftriaxone is not effective for treating syphilis *(2).* There have been preliminary studies of azithromycin for treatment of patients with primary and secondary syphilis but it is not currently recommended *(28).*

Physicians treating patients with syphilis should be aware of the Jarisch–Herxheimer reaction, which is a febrile reaction with chills, fevers, arthralgias, headache, and an increase in prominence of lesions. This is believed to be due to a release of treponemal constituents that occurs 4–6 h posttreatment and subsides within 24 h *(24).* Reassurance and aspirin or ibuprofen appear to alleviate the symptoms.

Follow-up is necessary to ensure that treatment of syphilis has been successful. The CDC recommends reevaluation of the patient clinically and serologically at 6 and 12 mo. Treatment failure is suspected in patients with primary or secondary syphilis who have nontreponemal antibody titers that have not decreased by two dilutions (fourfold) at 6 mo after therapy or who have persistent signs or symptoms. These patients should be retreated and evaluated for reexposure, HIV, or neurosyphilis *(2).* Unless reinfection is certain, a lumbar puncture should be performed in treatment failure *(2).*

There is a high probability that an infectious syphilitic individual will infect his or her partner during sexual activity (50%) *(25).* Persons who have been exposed within 90 d of the index case's diagnosis should receive presumptive treatment. Patients who were exposed >90 d prior to diagnosis should be evaluated and if serologic tests are not available immediately and follow-up is uncertain, presumptive treatment should be given *(2).*

There has been much debate on the optimal management of syphilis in HIV-infected patients. Although there are anecdotal reports of increased risk of treatment failure and increased incidence of neurosyphilis in HIV-positive patients, no randomized studies have proven this. In one multicenter, randomized, double-blind trial (541 patients), few clinical differences according to HIV status were noted *(29).* The serologic response of HIV patients was poorer, but there were few clinically defined failures in either group *(29).* CDC recommendations suggest treating HIV-positive patients with the same regimens as HIV-negative patients, but encourage closer follow-up. Clinical and serologic evaluation at 3, 6, 9, 12, and 24 mo is important in HIV patients *(2).* Some experts give additional treatment for primary and secondary syphilis in the HIV population, but it is not officially recommended. The CDC recommends that HIV-infected patients with either late latent syphilis or syphilis of unknown duration have a cerebrospinal fluid (CSF) examination before treatment *(2).*

All pregnant women with syphilis should receive penicillin appropriate to their stage of disease (Table 3). Owing to potential side effects in the fetus and erratic transplacental transfer, no antimicrobial agent other than penicillin is recommended, even in penicillin-allergic patients *(2,27).* The CDC recommends skin testing and desensitization in penicillin-allergic pregnant women with syphilis *(2).* A manifestation of Jarisch–Herx-

Table 3
Treatment of Syphilis

Stage	Drug	Dose	Duration	Comments
Primary/secondary	Benzathine penicillin G	2.4 million units i.m.	1×	
Nonpregnant penicillin allergic	Doxycycline or tetracycline	100 mg b.i.d.	2 wk	
		500 mg q.i.d.	2 wk	Close follow-up is essential.
	Desensitize against penicillin.	See above.		
Latent syphilis				
Early	Same as above			
Late	Benzathine penicillin G	2.4 million units i.m.	Three doses at 1-wk intervals	
Nonpregnant penicillin allergic	Doxycycline or tetracycline	100 mg b.i.d.	4 wk	
		500 mg q.i.d.	4 wk	
Tertiary syphilis	Aqueous crystalline penicillin G or	3–4 million units i.v. q4h (18–24 million units total)	10–14 d	
	Procaine penicillin plus probenecid (500 mg p.o. q.i.d.)	2.4 million units i.m. q.d.	10–14 d	
Penicillin allergic (both pregnant and nonpregnant)	Desensitize against penicillin.	See above.		

Data from ref. *2*.

heimer reaction is uterine contractions; therefore, some suggest fetal monitoring before initiation of penicillin therapy in patients in the third trimester *(27)*.

There is no documented evidence of *T. pallidum* resistance to penicillin *(25,27)*.

Other Genital Ulcerative Diseases

Granuloma inguinale and lymphogranuloma venereum (LGV) are rare diseases in the United States. Treatment with 100 mg of doxycycline twice a day for 3 wk is recommended; further information can be found in the recent CDC guidelines *(2)*.

HUMAN PAPILLOMA VIRUS

Human papilloma virus (HPV) infections have two important clinical manifestations: external genital warts (EGWs) and squamous intraepithelial lesions *(30)*. A discussion of these neoplasms is beyond the scope of this chapter but screening and treatment issues can be found elsewhere *(2)*. The majority of newly acquired HPV infections are asymptomatic. EGWs are diagnosed when visible warts occur in the genital area; they can be discrete or coalesce into confluent plaques *(30)*. The acetowhite test has not been definitely established as useful for diagnosis and has a low positive predictive value *(30)*. Biopsy is seldom needed and is reserved for atypical lesions; uncertain diagnosis; progression of disease during treatment; warts that appear pigmented, indurated, ulcerated, or fixed to underlying structures; or warts that are >1 cm^2.

An entire examination of the genitalia is warranted because EGWs frequently occur on multiple genital sites. Speculum examination assessing for vaginal and cervical warts is recommended for women with genital warts. Instrumentation (colposcopy, anoscopy, or urethroscopy) is recommended for women with cervical warts, men and women with recurrent perianal warts (history of anoreceptive intercourse), or men with warts at distal urinary meatus and terminal hematuria or abnormal stream *(31)*. The differential diagnosis of EGWs is broad and includes normal anatomic structures, acquired conditions (e.g., molluscum contagiosum), and neoplasms such as vulvar neoplasia *(2)*.

An estimated 24 million Americans are infected with HPV *(1)*. Surveillance systems for HPV are rudimentary, and some experts estimate the incidence of HPV infections to be closer to 5 million per year *(16)*. Genital HPV is transmitted primarily sexually; however, perinatal transmission can occur (laryngeal papillomatosis) *(2)*. Immunocompromised patients such as HIV-seropositive patients and renal allograft recipients are at high risk for genital HPV infection *(30)*. An association between increasing number of sex partners and detection of HPV has been noted *(32)*. There are inconclusive data on the association between smoking or estrogen stimulation (oral contraceptives or pregnancy) and HPV infection.

The 70 HPV genotypes are divided into low-risk types (including 6 and 11) and high-risk types (e.g., 16, 18, 31, 33, 35) based on their association with anogenital cancers *(30)*. Visible EGWs are caused by types 6 and 11 and have been associated with conjunctival, nasal, oral, and laryngeal warts *(2)*.

The primary goal of treatment of EGWs is to eliminate warts that cause physical or emotional distress *(30)*. There is no evidence that treatment eradicates HPV or decreases infectivity *(2)*. If left untreated, EGWs may resolve, remain unchanged, or increase in size. Patient education concerning such issues as HPV treatment and the

association of certain types of HPV infection to cancers is essential. Patients should be cautioned that several treatment sessions are often required to achieve a wart-free state. After clearance, patients should be advised to watch for recurrences. Annual cervical cytologic screening is recommended for all women whether or not they have EGWs. The presence of genital warts is not an indication for colposcopy *(2).*

Treatment is divided into patient-applied (podofilox and imiquimod) and provider-administered (cryotherapy, podyphyllin resin, trichloroacetic, or bichloroacetic acid [TCA/BCA] interferon and surgery) therapies (*see* Table 4). Podofilox and podyphyllin are antimitotic agents. Imiquimod is an immune-response–enhancing agent that induces interferon α and other cytokines. Cryotherapy with liquid nitrogen causes cryocytolysis resulting in sloughing and wart destruction. TCA/BCA are caustic agents that destroy warts by chemical coagulation of proteins. Owing to low viscosity of these agents, care must be taken to prevent "running" of the solution onto unaffected areas (treated areas should be allowed to dry before the patient sits or stands). Surgical removal includes curettage, eletrocautery/electrotherapy, and ablative therapy (laser). Intralesional injections of interferon have been shown to be effective while systemic and topical treatments have not. Cidofovir and 5-fluorouracil (5-FU/ipinephrine/bovine collagen gel) implants are under development.

There are no guidelines regarding which treatment to use first. Treatment of EGWs should be guided by patient preference and the patient's ability to follow directions, number and location of warts, and clinical expertise *(2).* Experts suggest that treatment should be changed or the patient referred to a specialist when three treatment sessions have resulted in no improvement, if there is incomplete clearance after six treatment sessions or when continued treatment extends beyond manufacturer's recommendations *(2,30).* Clinicians must monitor patient progress and avoid overtreatment. Most experts agree that combining modalities on a single wart does not increase efficacy *(2).* All wart treatments may cause mild local irritation, ulceration, or erosion. Ablative modalities can result in hypopigmentation, hyperpegmentation, or hypertophic scars. Pregnancy and immunodeficiency are associated with larger or more numerous EGWs *(30).* There are reports of immunocompromised patients having EGWs with high-risk types of HPV *(30,33).* Although current treatments are imperfect, most patients can eventually be wart free. There is no reported resistance for genital HPV currently.

DISEASES CHARACTERIZED BY URETHRITIS AND CERVICITIS

Neisseria gonorrhoeae and *Chlamydia trachomatis* cause the majority of urethritis and cervicitis. The etiology of most nongonococcal, nonchlamydial urethritis is unknown. Other agents that may cause urethritis include *Trichomonas vaginalis* and *Herpes simplex. Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* also have been implicated as causes of urethritis.

Urethritis

Urethritis refers to inflammation of the urethra in men or women and is manifested by dysuria, pyuria, or discharge. Discharge may range from scant and mucoid to grossly purulent. Although dysuria may suggest a urinary tract infection in females; in males, urethritis is usually due to STD. The CDC criteria for diagnosis of urethritis *(2)* are the presence of mucopurulent or purulent discharge, Gram stain of urethral

Table 4
Treatment of Genital Warts

Therapy	Dose	Duration	Comments	Cautions
Patient-applied				[a]
Podofilox	0.5% Solution/gel	Up to 4 cycles	Apply with finger or cotton swab. Apply b.i.d. for 3 d then 4 d of no therapy (one cycle)	[a]
Imiquimod	5% Cream	Up to 16 wk	Apply with finger 3 × a week.	[a]; Wash off 6–10 h after application.
Provider-applied				
Cryotherapy	Liquid nitrogen/cryoprobe	Repeat applications every 1–2 wk.		Avoid over- and underapplication. Avoid with cryoglobulinemia.
TCA/BCA	80–90%	Can repeat weekly.	Can use powder of sodium bicarbonate (baking soda) to remove excess.	
Podophyllin resin	10–25%	Can repeat weekly	Apply thin layer and allow to air dry. Wash area 1–4 h after application	[a]; Avoid over application and use on large wart area.
Office surgery (curettage, electrosurgery, and scissor excision)				
Alternative treatment				
Intralesional interferon			Can have flulike symptoms.	[a]; Avoid in transplant patients and those with psychiatric disease.
Laser surgery			May require general anesthesia.	

Data from ref. *2*.
[a] Safety in pregnancy is not established.

secretions demonstrating ≥5 white blood cells (WBCs) per oil immersion field, positive leukocyte esterase test on first-void urine, or microscopic examination of first-void urine demonstrating ≥10 WBCs per high-power field. The diagnosis of gonococcal urethritis depends on the demonstration of intracellular Gram-negative diplococci.

Although the symptoms and signs of gonorrhea (GC) and chlamydial infection overlap, GC is usually symptomatic, in contrast to chlamydial infection, which is often asymptomatic. In 90% of men with gonococcal urethritis, discharge occurs within 5 d of exposure *(34).* The discharge may be mucoid initially but becomes purulent and associated with dysuria within days. A copious, thick, green urethral discharge is more commonly associated with gonorrhea than with *Chlamydia.* In men, GC rarely spreads to the epididymis but may cause balantitis or penile swelling. Men with chlamydial infection present with pain on urination and discharge that ranges from clear to grossly purulent. Symptoms typically begin 7–10 d after a new sexual contact. Inguinal lymph notes are not enlarged or tender.

Both *Chlamydia* and GC are extremely common. In 1997, roughly 325,000 cases of GC and 527,000 cases of *Chlamydia* were reported to the CDC *(35).* Many cases of both diseases are not reported. Both infections are most prevalent in those 15–24 yr of age. These bacterial diseases, particularly GC, are more common in black populations, probably due to differences in access to care and other socioeconomic issues *(35).* Screening men for *Chlamydia* or asymptomatic GC has been particularly difficult, given the need in the past for a urethral swab. Currently, urine tests based on the detection of DNA by PCR or ligase chain reaction (LCR) are being used with greater success.

In most studies *C. trachomatis* has been associated with 30–50% of all cases of nongonococcal urethritis (NGU). It is also found in approx 20–30% of gonococcal urethritis. No clinical features reliably distinguish chlamydial and nonchlamydial NGU. In the absence of a positive culture for GC or *Chlamydia,* NGU is not believed to be caused by those two organisms. Evidence to support this belief includes the observation that neither *Neisseria gonorrhea* nor *Chlamydia* are isolated from the sexual partners of patients with culture-negative NGU. In addition, individuals with chlamydial NGU respond better to tetracyclines than those with nonchlamydial NGU. Although treatment with doxycycline suppresses symptoms of NGU in 90% of men, 35–50% of those with negative cultures for *Chlamydia* have persistent pyuria or urethral inflammation 6 wk after treatment. Persistence occurs in fewer than 20% of those with chlamydial NGU.

N. gonorrhoeae is a Gram-negative coccus. Culture remains the diagnostic test of choice because it is sensitive, inexpensive, and allows antibiotic susceptibility testing. A Gram stain of a urethral discharge typically shows the Gram-negative diplococci associated with neutrophils in ≥95% of symptomatic men with GC *(36).* Gram-negative diplococci seen extracellularly are considered equivocal. Approximately 50–70% of culture-positive asymptomatic men will have a positive Gram stain. Although advocated by some experts, Gram stains of endocervical discharge are rarely used to diagnose GC in women, but have been reported to be 40–60% sensitive and 95–100% specific.

DNA-based diagnostic tests, such as those based on the PCR and the LCR, are used less for diagnosis in symptomatic populations, given the utility and economy of Gram

stain and culture. They are proving to be extremely useful, however, in screening for GC and *Chlamydia* concomitantly in urine samples from high-risk asymptomatic individuals, who might not otherwise be tested.

Chlamydia trachomatis is an obligate intracellular pathogen. Therefore, diagnostic culture techniques are more difficult than those for *N. gonorrheae.* Of the three species recognized in the genus *Chlamydia—trachomatis, pneumoniae,* and *psittaci*—only the *trachomatis* species is associated with genital infection. Gram stain of the exudate from a patient with *C. trachomatis* NGU shows the presence of neutrophils but no intracellular.

The CDC's current treatment recommendations for urethritis are shown in Table 5. Although penicillin was the treatment of choice for *N. gonorrhoeae* for three decades, rapid spread of penicillinase-producing *N. gonorrhoeae* (PPNG) precipitated a need for alternative treatments. The CDC treatment guidelines for GC have been developed with regard to availability of medications and the resistance patterns in the United States. Because concomitant genital infection with *C. trachomatis* is common, treatment of patients with a positive Gram stain or culture for GC must be given treatment for both *N. gonorrhoeae* and *C. trachomatis.*

Chlamydial genital infection responds well to doxycycline. Azithromycin has been shown to eradicate *C. trachomatis* and alleviate symptoms. Some practitioners prefer its use when compliance is in doubt. Erythromycin is effective, but less so. It has been used extensively in pregnancy because of its safety profile. Clindamycin and ampicillin also have been used in pregnancy, although most authorities prefer ampicillin in pregnant woman who cannot tolerate the macrolides. For all types of urethritis discussed, patients with HIV infection should be treated the same as those without HIV infection.

Treatment of partners should be considered as important as treating the index case of urethritis. All recent (within 60 d) sexual contacts of patients with GC or chlamydial genital infection should be treated and, if possible, screened for STDs as well. This practice is designed to decrease the amount of time a person remains infectious, an effect that decreases the rate of secondary cases.

If noncompliance or reexposure is unlikely, individuals who remain symptomatic after treatment for NGU should be treated with 2 g of metronidazole orally in a single dose plus 500 mg of erythromycin base orally four times a day for 7 d, or 800 mg of erythromycin ethylsuccinate (EES) orally four times a day for 7 d.

Disseminated gonorrhea (DGI) occurs infrequently *(2).* Patients usually present with an asymptomatic mucosal infection, relatively mild systemic illness, asymmetric polyarthralgia, tenosynovitis, and a characteristic skin rash. Other patients present with suppurative arthritis and are less likely to have a rash or tenosynovitis *(37).* Recommended treatment is 1 g of ceftriaxone every 24 h, although cefotaxime, ceftizoxime, ciprofloxacin, or ofloxacin are alternative treatments. Therapy should be continued for 10–14 d *(2).*

Isolated reports of PPNG in the mid-1970s gave way to widespread PPNG by the 1980s, resulting in the abandonment of penicillin analogs as the drugs of choice for GC. Use of alternative agents including sulfa drugs, tetracyclines and most recently, quinolones has been followed by the development of resistance to these agents as well *(38).*

In 1986, the CDC established a surveillance program, the Gonococcal Isolate Surveillance Project (GISP), to monitor trends in the antimicrobial susceptibility of gono-

Table 5
Treatment of Urethritis and Cervicitis

Treatment of Urethritis or Cervicitis due to	For *Neisseria gonorrhea*	For *Chlamydia trachomatis*
Neisseria gonorrhea:	For *Neisseria gonorrhea* A single dose of: 400 mg Cefixime p.o. OR	For *Chlamydia trachomatis* 1 g Azithromycin p.o. in a single dose, OR 100 mg doxycycline p.o. b.i.d. for 7 d.
Because of a high association of *N. gonorrhea* with concomitant chlamydial infection, patients with gonorrhea should be treated for *Chlamydia.*	125 mg Ceftriaxone i.m. OR 500 mg Ciprofloxacin p.o. OR 400 mg Ofloxacin[a] p.o.	Alternative regimens: 500 mg Erythromycin base p.o. q.i.d. for 7 d OR 800 mg erythromycin ethylsuccinate p.o. q.d. for 7 d, OR 300 mg ofloxacin b.i.d. for 7 d If only erythromycin can be used and a patient cannot tolerate the high-dose regimens, the following can be used: 250 mg Erythromycin base p.o. q.i.d. for 14 d OR 400 mg erythromycin ethylsuccinate p.o. q.i.d. for 14 d
Chlamydia trachomatis	If Gram stain or culture does not show GC, the patient need only be treated for *C. trachomatis*	As listed above for treatment of *C. trachomatis*
Nongonococcal urethritis	No treatment required	As listed above for treatment of *C. trachomatis*

[a] Levofloxacin has not specifically been approved for the treatment of GC but is likely to be at least as effective as ofloxacin.
Data from ref. *2*.

coccal isolates in the United States *(39).* At each GISP clinic, urethral isolates are obtained from the first 20 men diagnosed with GC each month. These isolates are shipped to a regional laboratory, where the susceptibilities of the organisms are determined. Worldwide surveillance is performed by the World Health Organization (WHO) through a network of laboratories, entitled the Gonococcal Antimicrobial-Susceptibility Program (GASP) *(40).*

The best known form of β-lactam resistance for *N. gonorrhoeae* is plasmid mediated. Reports in the late 1980s led to the abandonment of ampicillin as the drug of choice for the treatment of gonorrhea. Surveillance has shown a decrease in the incidence of PPNG from about 15% in 1990 to <10% in 1995 *(41).* Resistance to β-lactams may also occur through chromosomal mutations. These usually produce low-level penicillin resistance, mediated through mechanisms other than β-lactamase production, such as an alteration in the penicillin binding proteins *(42,43).* Despite decreases in the incidence of PPNG, chromosomal β-lactam resistance has increased, as has plasmid-mediated high-level resistance to tetracycline *(41).*

Cases of GC caused by *N. gonorrhoeae* resistant to fluoroquinolones (QRNG) have been reported sporadically from many parts of the world, including North America *(44–46),* and are becoming widespread in parts of Asia *(35).* According to GISP (February 1997), QRNG is rare in the United States *(40,41).* In the United States during 1996, fewer than 0.05% of 4639 clinical isolates tested from surveillance laboratories had minimum inhibitory concentrations (MICs) >1.0 μg/mL to ciprofloxacin. As long as QRNG strains comprise <1% of all *N. gonorrhoeae* strains, fluoroquinolone regimens can be used with confidence *(2).* However, it is likely that importation and spread of QRNG will continue. As a result, the prevalence of QRNG in the United States could increase to the point that fluoroquinolones would no longer reliably eradicate gonococcal infections.

Tetracycline-resistant *C. trachomatis* was first described in 1990 with a report of five patients, four of whom experienced treatment failures *(47).* Isolates with this type of resistance formed 100-fold fewer inclusions in the presence of tetracycline than sensitive strains, suggesting that approx 1% of the isolates were resistant. Culture of a resistant organism in tetracycline-containing medium yielded a population that was uniformly tetracycline resistant. Isolates that survived continued serial passage became tetracycline sensitive again in antibiotic free medium. It appeared that not all organisms genetically capable of expressing the tetracycline resistance phenotype did so. This heterogeneous expression of tetracycline resistance is referred to as heterotypic resistance. The isolates found to be resistant to tetracycline were also resistant to doxycycline, erythromycin, sulfamethoxazole, and clindamycin but sensitive to rifampin, ciprofloxacin, and ofloxacin *(47).* In a follow-up study of adolescents who experienced relapse or reinfection, resistant isolates were found as often in those with repeated infections as those without recurrences, suggesting that the significance of resistance in clinical disease remains to be defined *(48).* Another tetracycline-resistant *Chlamydiae* has been isolated *(49).* This strain also appeared to display heterotypic resistance but differed in that it maintained sensitivity to erythromycin and azithromycin.

Fluoroquinolone resistance of an L2 reference strain has been reported only in laboratory-manipulated strains grown in subinhibitory concentrations of ofloxacin and

sparfloxacin after four rounds of selection *(50).* A point mutation in the *gyrA* quinolone-resistance-determining region of resistant strains was identified. However, clinical isolates have not been identified.

Cervicitis

Cervicitis refers to inflammation of the uterine cervix. The syndrome of mucopurulent cervicitis (MPC) is defined by mucopurulent or purulent discharge most often presenting as a vaginal discharge. Diagnosis of MPC is made when a swab reveals visible yellow or green discharge. Some but not all investigators consider cervicitis present if the endocervix is friable. Women with cervicitis due to GC or *C. trachomatis* may be asymptomatic, experience vaginal discharge, have lower abdominal discomfort, or present with an acute pelvic inflammatory disease characterized by moderate to severe lower abdominal pain and cervical motion tenderness. The most severe consequence of cervicitis is ascension of infection to the upper genital tract, resulting in infertility from obstruction of the fallopian tubes.

C. trachomatis, common in adolescent girls, is often asymptomatic and recurrent. It is recommended that all sexually active female adolescents be screened for *C. trachomatis (6).* High rates of chlamydial infection are found also in women ages 20–24 yr, particularly those with a new sexual partner. Both GC and *C. trachomatis* may cause cervicitis or MPC. Because a substantial number of cases remain symptomatic after treatment for those two organisms, there may be other etiologies as well. Treatment of cervicitis is summarized in Table 5. As is the case for urethritis, the sexual partners (within 60 d) of a woman with gonorrhea or chlamydial infection should be treated and if possible, screened to increase case finding.

Sexually Transmitted Pharnygitis

Despite pharyngeal HSV infection and the occasional isolation of *C. trachomatis,* sexually transmitted pharyngitis is almost synonymous with gonococcal pharyngitis. Gonococcal pharyngitis is relatively difficult to eradicate compared to genital tract infection. Although newer antibiotic regimens are better than previous ones, the cure rate remains less than that for uncomplicated GC genital infection. In one review, >95% of genital and rectal gonococcal infections were cured compared to only 83.7% of pharyngeal infections in women and 79.2% of pharyngeal infections in men *(51).* For this reason, the recommendations for therapy in pharyngeal GC do not include oral cefixime, which achieves lower levels than ceftriaxone given intramuscularly. Treatment of *C. trachomatis* should be initiated with treatment of pharyngeal gonorrhea because of the association of GC and *Chlamydia* in the genital tract. Recommended regimens include ceftriaxone, ciprofloxacin, and ofloxacin at doses recommended for the treatment of urethritis and cervicitis.

Epididymitis

Both *N. gonorrhoeae* and *C. trachomatis* may ascend the male genital tract to involve the epididymitis. Symptoms typically include unilateral pain that radiates to the testicle and tenderness with palpation. The differential diagnosis of epididymitis includes testicular torsion which is a surgical emergency. The recommended treatment of epididymitis is 125 mg of ceftriaxone intramuscularly plus 100 mg of doxycycline

orally twice daily for 10 d. A recommended alternative regimen is 300 mg of ofloxacin orally twice daily for 10 d *(2)*.

SEXUALLY TRANSMITTED PROCTITIS, PROCTOCOLITIS, AND ENTERITIS

Infection of the GI tract may occur from anal intercourse (proctitis) or sexual activity that includes fecal–oral contact (enteritis). Proctocolitis may occur with either route. Proctitis is characterized by anorectal pain, tenesmus, and rectal discharge and may be caused by GC, *C. trachomatis* including LGV strains or serovars, HSV, or *T. pallidum (2)*. Patients with acute proctitis who practice receptive anal intercourse should be examined with anoscopy to make a specific diagnosis. Although proctitis due to GC responds well to regimens recommended for uncomplicated GC infection, if pus is present on examination of the rectum, 125 mg of ceftriaxone intramuscularly plus 100 mg of doxycycline twice daily for 7 d is recommended. Rectal chlamydial infection due to the non-LGV serovars is unusual and probably responds to the regimens recommended for urethritis. LGV may cause a hemorrhagic proctitis associated with regional lymphadenitis. LGV is treated with 100 mg of doxycycline orally twice daily for 21 d or alternatively with 500 mg of erythromycin base orally four times daily for 21 d *(2)*.

DISEASES CHARACTERIZED BY VAGINAL DISCHARGE

Vaginitis and vaginal discharge are common complaints prompting women to visit their health care providers. The differential diagnosis is extensive and should include physiologic discharge, chemical or irritant vaginitis, atrophic vaginitis, and vaginitis due to the infectious agents discussed in the following sections. Many over-the-counter products, such as topical antifungals, are widely available and allow women to self treat, often inappropriately. This makes diagnosis even more difficult and confusing when patients present with partially treated disease.

Patients with vaginitis should undergo a speculum examination with careful examination of the cervix for discharge and acquisition of cultures *(2)*. If no cervical discharge is present, then the vaginal mucosa should be inspected and material obtained for pH as well as microscopic examination with normal saline and potassium hydroxide solutions. These simple bedside procedures should aid in determining whether or not a patient has an infectious etiology for vaginitis and guide further evaluation.

Bacterial Vaginosis

Signs and symptoms of bacterial vaginosis (BV) include a foul smelling, homogeneous, white, adherent vaginal discharge. Vulvovaginal pruritis, burning, and dysparenuria may be associated *(52)*. Diagnosis is usually based on clinical criteria which generally include any three of the following: (1) homogeneous, uniformly adherent discharge with little evidence of inflammation on examination; (2) vaginal fluid pH >4.5; (3) amine "fishy" odor after addition of 10% potassium hydroxide (KOH) solution to vaginal fluid; (4) presence of "clue" cells (epithelial cells with coarse granulation and bacterial studding along cell membrane) *(2)*.

Despite being the most common cause of vaginal discharge, the pathogenesis and mode of acquisition of BV are poorly understood. There is ample evidence that it is at least in part an STD. Risk factors for BV include multiple sexual partners, a new sexual partner, douching, and intrauterine device (IUD) as contraceptive method *(52).* Carriage rates are higher among sexually active women than in sexually inexperienced women *(52).* There appears to be no counterpart infection in men and there is no evidence that treatment of sexual partners is beneficial *(52).*

BV probably represents a disturbance of the balance of vaginal flora more than an actual infection *(52).* It arises when the normal flora, especially *Lactobacillus* species, are replaced by bacteria such as *Garderella vaginalis, Mycoplasma hominis, Prevotella* species, and anaerobes such as *Bacteroides* sp. *(52).*

Table 6 lists the recommended and alternative treatments of BV. Although the cure rates of the three regimens vary from 71% to 82% at 4 wk after treatment, all three are considered equally effective *(2).* Metronidazole, 750 mg p.o. q.d. for 7 d, has been approved for treatment of BV, but there are no data at this time comparing its efficacy to the regimens described previously *(2,52).* Recurrent BV is not uncommmon and the etiology of recurrences is yet to be determined *(52).* There are no reports of resistance at this time.

In the pregnant patient, BV is associated with adverse outcomes such as preterm labor, preterm birth, premature rupture of membranes, and chorioamnionitis *(52).* A recent randomized controlled trial has shown that pregnant women with BV had lower rates of preterm delivery when treated with metronidazole and erythromycin *(53).* The CDC recommends that women at risk for preterm delivery be screened for BV early in the second trimester and treated if positive (even if asymptomatic) (Table 6) *(2).* Treatment of low-risk asymptomatic women is controversial. Intravaginal clindamycin cream should be avoided in pregnancy because of evidence of increased risk of preterm delivery *(2).*

Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis.* Classically, infection is associated with a thin, greenish-yellow vaginal discharge, dysparenia, vaginal irritation, and sometimes dysuria *(54).* On examination, a thin vaginal discharge along with punctate cervical hemorrhages (strawberry cervix) is characteristic. Men are frequently asymptomatic although trichomoniasis may cause prostatitis and epididymitis *(54).*

Although clinical examination alone is not usually sufficient to establish a diagnosis, motile trichomonads seen on a wet mount are considered diagnostic. Unfortunately, sensitivity of wet mount examination is only about 60% in women and 50–90% in men *(54).* Although culture remains the gold standard of diagnosis, recent studies show that detection by PCR is very sensitive (97%) and specific (98%) *(55).*

T. vaginalis infection is the most common nonviral STD in the United States *(16).* Although trichomonads can survive for up to 45 min outside the human body, the consensus view is that *T. vaginalis* is transmitted sexually *(54).* Risk factors for trichomoniasis include multiple sexual contacts and low socioeconomic status *(54).* Trichomoniasis has been associated with vaginal cuff cellulitis after abdominal hys-

Table 6
Treatment of Vaginitis

Vaginitis	Drug	Dose	Duration	Comments
Bacterial	Metronidazole	500 mg p.o. b.i.d.	7 d	
	OR			
	Metronidazole vaginal gel	0.75% b.i.d.	5 d	
	OR			
	Clindamycin vaginal cream	2% qhs	5 d	
Alternative	Metronidazole	2 g p.o.	1×	
	OR			
	Clindamycin	300 mg p.o. b.i.d.	7 d	
Pregnancy	Metronidazole	250 mg p.o. t.i.d.	7 d	
Alternative	Metronidazole	2 g p.o.	1×	
	OR			
	Clindamycin	300 mg p.o. b.i.d.	7 d	
	OR			
	Metronidazole intravaginal gel	0.75% b.i.d.	7 d	Low risk only as there is no systemic treatment.
T. vaginalis	Metronidazole	2 g p.o. qd	1×	
Alternative	Metronidazole	500 mg p.o. b.i.d.	7 d	
Candidiasis	Fluconazole	150 mg p.o.	1×	
	OR			
	Intravaginal creams			
	Butoconazole 2%	5 g qhs	3 d	
	OR			
	Clotrimazole 1%	5 g qhs	7–14 d	
	OR			
	Miconazole 2%	5 g qhs	7 d	
	OR			
	Terconazole 0.8%	5 g qhs	3 d	
	OR			
	Terconazole 0.4%	5 g qhs	7 d	
	OR			

(continued)

Table 6 (continued)

Vaginitis	Drug	Dose	Duration	Comments
	Vaginal suppositories			
	Miconazole	200 mg qd	3 d	
	OR			
	Miconazole	100 mg qd	7 d	
	OR			
	Terconazole	80 mg qd	3 d	
	OR			
	Nystatin	100,000 U qhs	14 d	
Recurrent VVC	Clotrimazole	100 mg qd	7 d	
	OR			
	Clotrimazole	100 mg 2 tablets qd	3 d	
	OR			
	Clotrimazole	500 mg	1×	
	OR			
	Ointment			
	Tioconazole 6.5%	5 g	1×	
	Induction Choose one of the above for induction then start maintenance.		14 d	Continue until patient is asymptomatic and cultures negative.
	Maintenance			
	Ketoconazole	100 mg p.o. qd	6 mo for all listed	
	Itraconazole	50–100 mg p.o. qd		
	Fluconazole	100 mg q p.o. week		
	Clotrimazole suppositories	500 mg intravaginally q w		

Table 6
Treatment of PID

Type of Treatment	Duration	Comment
Inpatient Regimen 1 2 g Cefotetan intravenously (i.v.) q12h or 2 g cefoxitin i.v. q6h PLUS 100 mg Doxycline i.v. q12h	Continue for a least 48 h after the occurrence of significant clinical improvement. Doxycycline should then be given orally for a total of 14 d.	
Regimen 2 900 mg Clindamycin i.v. q8h PLUS gentamicin 2 mg/kg IV/IM loading dose then 1.5 mg/kg q8 (can substitute with single dosed Gentamicin)	Continue for at least 48 h after clinical improvement. Doxcycline 100 mg (as above) or clindamycin, 450 mg orally 4 × a day should be given until d 14 of treatment.	
Alternative in patient 400 mg Ofloxacin i.v. q12 h PLUS 500 mg metronidazole i.v. q8h. OR 3 g Ampicillin/sulbactam i.v. q6h PLUS doxyclycline (as above) OR 200 mg Ciprofloxacin i.v. q12h PLUS doxycline (as above) PLUS 500 mg metronidazole i.v. q8h	Same principle as above	These regimens have been studied less intensely but offer broad coverage.
Outpatient Regimen 1 400 mg Ofloxacin p.o. b.i.d. PLUS 500 mg metronidazole p.o. b.i.d. × 14 d	Continue both for 14 d	
Regimen 2 2 g Cefoxitin intramuscularly (i.m.) PLUS 1 g probenecid orally concurrently in a single dose, OR 250 mg ceftriaxone i.m. in a single dose OR another third-generation cephalosporin plus 100 mg Doxycycline p.o. b.i.d. × 14 d	Continue doxycycline for 14 d.	

terectomy, as well as premature rupture of membranes, preterm infants, and low-birthweight infants *(54)*.

Treatment is limited and consists of metronidazole (*see* Table 6). Sexual partners should be treated and patients should refrain from sexual contact until cured. After the first trimester, infected pregnant women should be treated with a single dose of metronidazole (2 g) *(2)*. A dose of 100 mg of clotrimazole intravaginally once a day for 2 weeks (response rate is ~25%) can be used during the first trimester for symptomatic relief until the patient can be safely treated with metronidazole *(54)*. Owing to unacceptable failure rates, previously proposed topical therapies are not recommended *(2)*. Women with allergies to metronidazole should undergo desensitization *(2)*.

Although exact data on the frequency of resistant trichomoniasis is lacking, Sobel et al. reported a 17-fold increase in the rate of metronidazole resistance *(56)*. The mechanisms of resistance are not known but in some cases can be overcome with larger doses and longer duration of metonidazole therapy *(54)*. For persistent infection in a compliant patient, an oral regimen lasting 10–14 d (metronidazole 2–4 g daily) *(57)* combined with intravaginal metronidazole has been advocated *(54)* and the CDC recommends 2 g of metronidazole q.d. for 3–5 d *(2)*. There are numerous case reports on alternative treatments for resistant trichomoniasis but no case-controlled studies. One patient with persistent infection was successfully treated with a combination regimen of oral and intravaginal tinidazole (500 mg orally q.i.d. plus 500 mg intravaginally b.i.d.) for 14 d *(58)*. Paromomycin cream may to be useful for cases of metronidazole resistance or in cases of metronidazole allergy *(59)*.

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) caused by *Candida albicans* typically presents with a vaginal discharge that is thick, white, adherent to vaginal walls, and cottage cheese like in consistency *(60)*. VVC is frequently accompanied by vulvar pruritus as well as dysuria, dysparenuria, and vaginal burning *(61)*. While these are considered the "classic" findings of *C. albicans* infection, it is important to note that some patients will present atypically, making diagnosis by history and physical examination alone problematic.

In addition to the history and physical examination, workup of suspected VVC should include a speculum examination and microscopic examination of the vaginal discharge or secretions *(60)*. The specimen for microscopy should be examined both in normal saline and in KOH solution. Specimens from patients with *C. albicans* infection will typically reveal either yeast or pseudohyphae, in addition to large numbers of white blood cells *(60)*. *C. glabrata (Torulopsis)* infection is characterized by only budding yeast (no hyphae) *(61)*. If no yeast, pseudohyphae, or other findings suggestive of noncandidal infection are seen (clue cells, motile trichomonads, etc.), then sending material for culture is recommended *(60)*. Measurement of vaginal pH is useful because the vaginal pH in VVC is <4.5 and if elevated could indicate a mixed infection *(60)*.

It is estimated that 75% of women will have at least one episode of VVC in their lifetimes *(60)*. Risk factors for developing VVC include pregnancy, diabetes mellitus, recent treatment with broad-spectrum antibiotics, and corticosteroid use *(60)*. The incidence of VVC is increased in the second decade and peaks in the third and fourth decades of life *(60)*. Sporadic VVC usually occurs without a precipitating factor with

the exception of uncontrolled diabetes. There appears to be an alleged increase in incidence of VVC in HIV-infected women; prospective controlled studies are underway to confirm this *(2,60).* The role of sexual transmission in VVC remains unknown and treatment of sexual partners is not recommended at this time *(2,60).*

C. albicans is isolated in an estimated 80–90% of cases of VVC and the remaining number of cases are due to other species, especially *C. glabrata (60,61).* Infrequent causes of fungal vaginitis include *C. parapsilosis* and *C. tropicalis (60).* VVC can be divided into uncomplicated infection which occurs in normal hosts, is mild to moderate in severity, and is caused by *C. albicans (2).* This type of infection responds to the topical azoles and oral therapy as listed in Table 6 (including short duration therapy). Complicated candidiasis with moderate to severe infection requires longer courses of therapy (10–14 d). Predisposing risk factors include uncontrolled diabetes, immunosuppression, history of recurrent vulvovaginal candidiasis, and antibiotic therapy *(2,61).*

Patient preference should influence the choice of treatment of VVC. A variety of effective topical azole agents are available and there is no strong evidence that one formulation has superior cure rates over the other. Oral systemic azole agents achieve comparable therapeutic cure rates; however, only fluconazole is recommended by the CDC at this time *(2).* HIV-positive women with either *C. albicans* or *C. glabrata* vaginitis should be managed in the same fashion as the HIV-negative population *(2).* For pregnant patients, a 7-day course of topical butoconazole, clotrimazole, miconazole, or terconazole is recommended *(2).*

Fewer than 5% of women experience severe or recurrent VVC infections, defined as more than four episodes in a 12-mo period *(2).* Only a minority of women have apparent risk factors such as uncontrolled diabetes and immunosuppression. Prior to initiating therapy for recurrent VVC, a vaginal culture should be obtained to identify noncandidal species that may require different therapy *(60).* First, patients should receive induction therapy (a 14-d course of an agent in Table 6) to achieve negative vaginal cultures and then a maintenance regimen should be instituted for 6 mo *(2,61).*

Resistant *C. albicans* causing vaginitis is rare. High-level resistance to fluconazole and cross-resistance to ketoconazole and itraconazole occurred in a patient who had previously been treated for 1 mo with fluconazole *(62).* The patient responded to treatment with boric acid intravaginally (600 mg b.i.d.) for 2 wk *(62).* Most clinically resistant VVC appears to be with non-*albicans* species, particularly with *C. glabrata.*

In a recent double-blind, placebo-controlled trial involving HIV-positive women, the use of fluconazole weekly was effective in reducing *C. albicans* isolation by 50%. However, simultaneous increase in non-*albicans Candida* species (primarily *C. glabrata*) developed *(63).* Selection of more resistant species in patients exposed to fluconazole is a concern.

Very little information regarding optimal treatment of *C. glabrata* is available. *C. glabrata* isolates have intrinsic reduced susceptibility to all azoles *(61).* Short course treatment regimens should not be used with *C. glabrata,* and azole regimens should only be tried if the patient is treatment naïve *(61).* Other regimens include 600 mg of boric acid vaginal suppositories per day for 14 d or flucytosine cream intravaginally once daily for 14 d *(61).* Risk factors specifically for *C. glabrata* vaginitis include

advanced age, underlying disease such as diabetes mellitus, and recent exposure to azoles *(61).* VVC due to *C. glabrata* should be included in the differential diagnosis for any woman with recurrent yeast infections or in whom infection repeatedly fails to resolve despite compliance.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) remains a diagnostic and treatment challenge. It is typically defined as an infection of the female genital tract above the cervix and may include salpingitis, endometritis, tubuloovarian abscess (TOA), and/or frank peritonitis *(64).* Long-term sequelae of PID are severe and include ectopic pregnancy, infertility, and chronic pelvic pain *(64).* In the United States, the population most commonly affected by PID appears to be the young, nonwhite, unmarried urban dweller as well as those with a history of PID, multiple sexual partners, previous or current STDs, and cigarette smoking *(64).* Controversy surrounds the role of IUDs and douching as risk factors for PID *(64).*

The diagnosis of PID is imprecise and should be considered in any woman with pelvic pain. Definitive diagnosis can be made by culture of involved areas, but this frequently involves invasive procedures such as culdocentesis, endometrial biopsy, and/or laparoscopy. The differential diagnosis is extensive, and should include ectopic pregnancy, ovarian torsion, flare of endometriosis, ruptured ovarian cyst, appendicitis, cholecystitis, colitis, gastroenteritis, pyelonephritis, nephrolithiasis, and bowel perforation. The CDC recommends initiating antibiotic therapy for PID in patients with adnexal, lower abdominal or cervical motion tenderness *(2).* The presence of fever, an elevated erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP), and cervical or vaginal discharge with proven chlamydial or gonorrheal infection support the diagnosis of PID *(2).* The findings of hydrosalpinx, pyosalpinx with thickened tubular walls with or without free fluid in the pelvis, or tuboovarian complex are considered to definitively establish a diagnosis of PID *(2).*

C. trachomatis and *N. gonorrhea* are well-documented causes of PID. One recent randomized, controlled trial found that identifying and treating women with chlamydial cervical infections reduced the incidence of PID *(65).* PID is frequently a polymicrobial infection with bacteria such as *M. hominis, H. influenzae, G. vaginalis,* staphylococci, Group B streptococci, *E. coli,* and anaerobes *(66).* Thus, the consensus is that PID necessitates broad-spectrum antibiotic therapy. Anaerobes are particularly frequent in women with TOA and with PID in the presence of HIV infection or bacterial vaginosis *(64,66).* There is an association between bacterial vaginosis and PID, but its significance is controversial.

Given the serious consequences of PID, prevention and early treatment should be a priority. The CDC recommends hospitalization for patients who are pregnant, immunocompromised, noncompliant, failing outpatient regimens, not tolerating oral antibiotics, or who have a TOA or in whom a surgical cause cannot be excluded *(2).* Table 7 lists the CDC's treatment recommendations for PID. All patients, whether treated on an inpatient or outpatient basis, should have follow-up within 3 d of initiation of therapy. If no improvement is noted on appropriate treatment, then additional testing, other diagnoses, or surgical referral should be considered *(2).* Evaluation of male sexual partners of patients with PID is an essential component to treatment.

SEXUALLY TRANSMITTED ECTOPARASITIC INFECTIONS

Ectoparasitic infestations are common worldwide and can be endemic. In the United States, both scabies and *Pediculosis pubis* (crab lice) are predominately sexually transmitted *(67).* An in-depth discussion of these infestations can be found in a recent monograph by Meinking *(68).* Lindane, a drug used for both scabies and crab lice, should be used cautiously because there are reports of central nervous system (CNS) toxicity and death. The CDC recommends that lindane not be used immediately after bathing, as this increases its absorption, and also not prescribed for persons with extensive dermatitis or for pregnant women or children <2 yr of age *(2).*

Pediculosis pubis

Crab lice may infest the pubic and perianal areas and can extend to the beard, axilla, and eyelashes (phthiriasis palpebrarum). Treatment should be applied to all hairy areas of the body. The CDC recommends 1% permethrin cream (synthetic pyrethroid), 1% lindane shampoo (organochlorine), or pyrethrins with piperonyl butoxide (plant extract) *(2).* Brown reviewed previous trials and concluded that permethrin was more effective than lindane *(67).* Cure rates of 60% and 57% respectively have been reported for single treatment with 1% lindane and 1% permethrin *(68).* Reportedly, a second treatment 1 wk later will increase the cure rate to 86% and 72%, respectively *(68).* A 93% cure rate with a single treatment of 5% permethrin has been reported *(68).*

Scabies

The CDC recommends 5% permethrin cream (wash off 8–14 h later) for the treatment of scabies. An alternative regimen is 1% lindane (8-h application) or 6% sulfur (apply nightly for three nights) *(2).* Patients, especially those who are HIV-positive, can develop crusted scabies (Norwegian Scabies). Recommended treatment is with 200 mg/kg of ivermectin single dose in immunocompetent patients and two doses in immunocompromised patients *(68).*

There are two major forms of resistance reported against insecticides: target-site resistance (insecticide no longer binds to target) and detoxification enzyme-based resistance which occurs when enhanced levels or modified activities of esterases, oxidases, or glutathione-*S*-transferases prevent the insecticide from reaching its site of action *(69).* Pyrethroid (permethrin) resistance appears to be emerging in the form of target-site resistance known as a knockdown resistance gene *(kdr).* The *kdr* appears to be unaffected regardless of the concentration of permethrin *(68).* Lindane resistance in scabies has been reported in the United States and lindane resistance is reported as "commonplace" in Peru *(68).* If a patient is not cured after a second treatment with a product, then treatment should be changed to a drug with a different active ingredient in case the organism is resistant.

OTHER CONSIDERATIONS

Hepatitis A and hepatits B can be transmitted sexually. Hepatitis and other viral illnesses such as HIV are discussed elsewhere in this book. As part of prevention and risk reduction, at-risk individuals should be counseled to receive hepatitis B Virus (HBV) vaccination *(6).*

Key Points

- STD management must include screening and treatment of sexual partners to prevent transmission and severe complications.
- The CDC guidelines are readily available and provide the current standard for therapy of STDs.
- Earlier case detection is crucial for disease control; thus, rapid diagnostic testing should be used when available.
- Prevention of STDs must be emphasized as concurrent STDs facilitate the transmission of HIV and viral STDs are incurable.

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12
Gastrointestinal Tract Infections

Laurie Haas and Luis Marsano

Patients with infections of the gastrointestinal (GI) tract may present with a range of complaints from vague symptoms such as malaise and anorexia to more serious manifestations such as severe diarrhea and sepsis. Although many GI infections require antibiotic therapy, others cause self-limited disease and only supportive care is needed. In the last decade, the recognition of the clinical importance of *Helicobacter pylori* and its cause and effect on peptic ulcer disease has changed what was once thought to be a disorder of excessive acid production to an infectious disease. The rising incidence of hepatitis C virus and progression to chronic active hepatitis and cirrhosis has also placed a tremendous burden on the health care system to find more effective and tolerable therapies for this disease. The emergence of resistance to antibiotics used to treat many of these infections, especially *Helicobacter pylori* infection and infectious diarrheal syndromes, poses new challenges for clinicians.

ESOPHAGEAL INFECTIONS

Esophageal infections have increased in frequency over the last decade, in part as a result of the growing numbers of patients with acquired immunodeficiency syndrome (AIDS) and organ transplantation requiring immunosuppressive therapy. Patients with esophageal infections may be asymptomatic; however they more commonly present with symptoms of dysphagia (difficulty in swallowing) or odynophagia (painful swallowing). Rarely does esophageal infection progress to more serious complications such as hemorrhage, fistula formation, or stricture. Without predisposing factors, esophageal infection is uncommon in immunocompetent adults. Risk factors in otherwise healthy adults may include recent antibiotic use, impaired esophageal peristalsis, or trauma. Most commonly, some form of humoral or cellular immunodeficiency underlies the esophageal infection. These conditions include AIDS, cancer and cancer chemotherapy, or corticosteroid use or other immunosuppressive therapy *(1)*.

Fungal Infections

The most common cause of fungal infection of the esophagus is *Candida albicans*. *Candida* esophagitis occurs most commonly in immunocompromised individuals. Physical examination may be useful if oral candidiasis is present; however, upper gastrointestinal endoscopy may be necessary to confirm the diagnosis. In AIDS patients

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with oral candidiasis, the presence of odynophagia or dysphagia most often indicates *Candida* esophagitis. Therefore, therapy can be instituted without endoscopic evaluation *(2)*. *Aspergillus* is the second most common cause of fungal esophagitis. It occurs most frequently in cancer patients, who usually present with severe odynophagia. Less common fungal infections include histoplasmosis and blastomycosis. These patients most often present with dysphagia. Although esophagitis with these latter pathogens is uncommon, the diagnosis should be considered in cases where presumed *Candida* esophagitis does not respond to therapy. Upper GI endoscopy and culture or histopathology is necessary to confirm the diagnosis *(1)*.

Oral therapy with 200 mg of fluconazole on d 1 followed by 100 mg once daily, 400 mg of ketoconazole once a day, or 100 mg of itraconazole oral solution twice a day for 14 d is effective for treatment of esophageal candidiasis *(3)*. Although clotrimazole and miconazole may be effective for prophylaxis, these therapies are less effective for active esophageal infection. Patients who are resistant to treatment with fluconazole may be treated with low dose amphotericin B. Flucytosine may be given in combination with itraconazole or amphotericin B in those patients with infections resistant to fluconazole *(4)*. Systemic aspergillosis should be treated with high-dose amphotericin B or itraconazole. Itraconazole is the treatment of choice for esophagitis due to histoplasmosis.

The azoles have largely replaced the use of other antifungal agents in the management of both oral and esophageal candidiasis. Although fluconazole remains the first-line therapy, there is evidence of increasing antibiotic resistance, especially in the AIDS population. Risk factors for developing resistance include previous exposure to therapy, both the number of treated episodes and duration of therapy, as well as the degree of immunosuppression *(5)*. Alternative first-line therapies to consider for oral candidiasis include 3 mL of nystatin q.i.d. for 21 d *(6,7)* as well as the chlorohexidine-containing mouth rinses. The effectiveness of preventing or treating esophageal candidiasis with these therapies in immunocompromised patients requires further testing.

Viral Infections

The viruses most likely to invade the esophagus include herpes simplex virus (HSV), cytomegalovirus (CMV), and varicella zoster virus (VZV). HSV is second to *Candida* as a cause of esophagitis *(1)*. While esophagitis occurs most commonly in immunocompromised individuals, HSV has been reported in immunocompetent patients. CMV esophagitis, however, rarely occurs in immunocompetent patients. Patients usually present with dysphagia or odynophagia. Endoscopy is necessary to confirm the diagnosis. While VZV is a recognized cause of viral esophagitis, it is unknown what the frequency of esophageal involvement is during the course of chickenpox.

Analgesia with viscous lidocaine suspension may be the only treatment necessary in immunocompetent individuals with HSV esophagitis. Acyclovir may shorten periods of viral shedding, lessen pain, and hasten healing in immunocompromised individuals. Administration of 5 mg/kg of ganciclovir, b.i.d. or 90 g/kg bid of foscarnet b.i.d. for 21 d is effective in treating CMV esophagitis *(8,9)*.

Mycobacteria

Previously tuberculous involvement of the esophagus once was considered rare; however, reported cases have increased owing to the increased evidence of AIDS in the population. Tuberculosis most commonly affects the middle third of the esophagus as a result of spread from regional lymph nodes. Patients may present with dysphagia or odynophagia, and the most common complication is tracheoesophageal fistula.

Treatment for tuberculous involvement in the esophagus should follow guidelines for treatment of tuberculosis, including multidrug therapy *(1,10).* Awareness of the rising frequency of isoniazid (INH)-resistant and multidrug-resistant tuberculosis is important and therapy should be guided by results of susceptibility testing (*see* Chapter 9).

Bacterial Infections

Bacterial esophagitis is uncommon and usually follows esophageal trauma from nasogastric tube placement, radiation, or gastroesophageal reflux disease (GERD). It may also be diagnosed in neutropenic patients undergoing chemotherapy. The common organisms include *Streptococcus viridans* and *Staphylococcus* and *Bacillus* species. Infection with *Actinomyces israelii, Corynebacterium diphtheriae,* and *Lactobacillus acidophilus* have also been reported. Endoscopy is required to confirm the diagnosis *(1,10).* Therapy should be tailored to the drug sensitivities of the cultured organisms.

GASTRIC INFECTIONS

Helicobacter pylori

The discovery of *Helicobacter pylori* has dramatically transformed the approach to diagnosis and treatment of peptic ulcer disease. It is now known that *H. pylori* accounts for >70% of duodenal ulcers, 60–90% of gastric ulcers, and is also a cause of atrophic gastritis. *H. pylori* is also found in nearly 100% of individuals with chronic active gastritis. In addition, *H. pylori* has been classified as a type I carcinogen by the World Health Organization and has a strong association with gastric cancer and lymphoma. *H. pylori* is a helical Gram-negative rod that produces a variety of enzymes that help the organism adapt to its acidic environment. It is found only in gastric epithelium; however, it can be found in other areas of the gastrointestinal tract secondary to gastric metaplasia *(11).*

H. pylori is found worldwide, with a higher incidence in underdeveloped and third world countries. It is reported that two-thirds of the world's population is infected with *H. pylori* and random testing of blood donors reveals that the prevalence in the general population in the United States is around 50%. The transmission of *H. pylori* is via the fecal–oral route. Symptoms of infection with *H. pylori* may include those associated with gastritis or peptic ulcer disease, such as epigastric pain, bloating, early satiety, nausea, and vomiting. Many individuals, however, are asymptomatic.

There are several tests available to detect infection with *H. pylori.* These include serology, urea breath test, or endoscopy with biopsy to perform both rapid urease test and culture. Serology has limited usefulness to detect active infection and may remain positive even after eradication of the bacteria has been achieved *(11).*

Table 1
Current Treatment Options for *H. Pylori* Infection

OC	40 mg Omeprazole p.o. qd + 500 mg clarithromycin t.i.d. × 2 wk, then 20 mg omeprazole p.o. qd × 2 wk	Efficacy: 70–75%
RC	400 mg Ranitidine bismuth citrate (RBC) b.i.d. + 500 mg clarithromycin t.i.d. × 2 wk, then 400 mg RBC b.i.d. × 2 wks	Efficacy: 73–84%
BMT	525 mg Bismuth subsalicylate (Pepto Bismol®) q.i.d. + 250 mg metronidazole q.i.d. + 500 mg tetracycline q.i.d. × 2 wk + H_2RA therapy × 4 wk	Efficacy: 88–90% With omeprazole 84–92%
LAC	30 mg Lansoprazole b.i.d. + 1 g amoxicillin b.i.d. + 500 mg clarithromycin t.i.d. × 10 d	Efficacy: 92%
LA	30 mg Lansoprazole t.i.d. + amoxicillin 1 g t.i.d. × 2 wk (restricted labeling for those who are allergic or intolerant of clarithromycin)	Efficacy: 50–60%
RC	400 mg Ranitidine bismuth citrate (RBC) b.i.d. + 500 mg clarithromycin b.i.d. × 2 wk, then 400 mg RBC b.i.d. × 2 wk	Efficacy: 75%
OAC	20 mg Omeprazole b.i.d. + 500 mg clarithromycin b.i.d. + 1 g amoxicillin b.i.d. × 10 d	Efficacy: 86–95%
LAC	30 mg Lansoprazole b.i.d. + 500 mg clarithromycin b.i.d. + 1 g amoxicillin b.i.d. × 10 d	Efficacy: 86–91%
MOC[a]	20 mg Omeprazole b.i.d. + 500 mg metronidazole b.i.d. + 500 mg clarithromycin b.i.d. × 7 d	Efficacy: 89%
MOA[a]	20 mg Omeprazole b.i.d. + 1 g amoxicillin b.i.d. + 500 mg metronidazole b.i.d. × 7 or 10 d	Efficacy: 75–83%
RCA[a]	400 mg RBC b.i.d. + 500 mg clarithromycin b.i.d. + 1 g amoxicillin q.i.d. × 10 d	Efficacy: 62–75%

[a] Not FDA Approved.
Data from refs *10–13*.

Multiple drug regimens are effective for eradication of *H. pylori* (Table 1). Individuals who should be treated for *H. pylori* are those with peptic ulcer disease who are *H. pylori* positive, ulcer patients in remission who also test positive for *H. pylori,* and those with mucosal-associated lymphoid tissue (MALT) lymphoma. Patients with a first-degree relative who has gastric carcinoma should also be considered for therapy. In patients with complicated ulcer disease or MALT lymphoma, eradication should be confirmed by urea breath test or biopsy 1 mo after completion of therapy.

Compliance with treatment regimens is a very important issue, and there is evidence for emerging antibiotic resistance to *H. pylori.* Metronidazole resistance is common worldwide and clarithromycin resistance is increasing in many regions. Although resis-

tance has been shown to effect cure rates of therapy in some studies, data remain scarce and the clinical impact of resistance is unclear *(16)*. Most triple-drug-based therapies containing the proton pump inhibitors as well as two antibiotics remain highly effective for eradication. Methods for routine culture of *H. pylori* and sensitivity determination have not been established in many hospitals, and access to these remains predominantly in academic centers. Consideration for determination of resistance should be restricted to those individuals who do not respond to primary therapy *(15)*. Noncompliance with treatment regimens remains problematic and further increases the risk of antimicrobial resistance. At this point in time, there are no recommendations regarding treatment of those individuals with nonulcer dyspepsia. A drawback of using empiric therapy is the potential for development of resistance *(11)*.

Other

CMV is the next most common infectious etiology of gastritis. It has been reported in healthy individuals; however, it is more common in those who are immunocompromised. Rarely gastritis occurs as a result of HSV infection or syphilis. The only fungal infection that is recognized to occur in the stomach is histoplasmosis. Treatment for this should be approached as for other gastrointestinal organs *(11)*.

INFECTIONS OF THE INTESTINE (SMALL AND LARGE)

Infectious Diarrhea

Infections in the small and large intestine can present in a number of ways, making the diagnosis difficult. Symptoms may include malaise, fever, headache, and abdominal pain. Diarrhea, however, is the most widely recognized marker of intestinal infection including both small bowel and colon. Classification of diarrhea is usually based on symptom duration and may be acute (lasting <3 wk) or chronic (lasting >3 wk). Diarrhea can also be classified by pathophysiological type, including osmotic (due to ingestion of poorly absorbed solutes) or secretary (due to inhibition of ion absorption or stimulation of ion secretion). Diarrhea of small bowel origin is usually characterized by a small number of voluminous stools. In contrast, small volume stools, possibly containing blood, pus, or mucus are more characteristic of colonic involvement *(17)*.

Virus

Norwalk virus and Norwalk-like viruses account for 40–60% of acute viral gastroenteritis occurring in older children and adults. Symptoms typically last 12–48 h and treatment is supportive. Rotavirus is another common cause of diarrhea and accounts for >60% of diarrhea seen in children under the age of 2. In contrast to Norwalk virus, symptoms may last for 3–10 d. Diagnosis of rotavirus can be made by detection of antigen in the stool. Treatment is also supportive; however, an oral hydration solution is often needed if dehydration does occur *(17)*. HSV and CMV are important causes of proctitis in homosexual men (*see* Chapter 11). Other viruses that less frequently cause diarrhea include adenovirus, coronavirus, astrovirus, and calicivirus.

Traveler's Diarrhea

Symptoms of traveler's diarrhea include mild abdominal cramping and diarrhea characterized by three to five watery bowel movements a day. Fever may occur in 10%

of individuals. Endemic areas for traveler's diarrhea include Latin America, Africa, the Middle East, and Asia. The single most important agent is enterotoxigenic *E. coli* (ETEC) followed by *Salmonella* (nontyphi) and *Shigella.* Rotavirus, Norwalk virus and other enteric viruses may be etiologic. *Giardia* and *Cryptosporidia* have also been reported in a small percentage of patients *(17).* Antimicrobial resistance in the normal flora frequently develops in travelers to developing countries, even when symptoms do not occur. Although trimethoprim–sulfamethoxazole, doxycycline, tetracycline, and nalidixic acid have been used for many decades as first-line therapy for traveler's diarrhea, near complete resistance of organisms to these therapies in many countries has led to the increased use of fluroquinolones *(18).*

For mild symptoms, bismuth or loperamide to control diarrhea and supportive care are adequate. For more severe illness, 500 mg of ciprofloxacin b.i.d., 400 mg of norfloxacin b.i.d., or 300 mg of ofloxacin b.i.d. for 3 d are effective. Metronidazole in a dose of 250 mg b.i.d. for 7 d may also be used *(19).*

Food Poisoning

Food and water are common vehicles for transmission of organisms. Although bacteria account for the majority of cases of food poisoning, parasitic and viral agents may also cause illness. In the United States, *Salmonella* infection is the primary cause of foodborne illness while *Clostridium perfringens* accounts for most food poisoning worldwide. Other bacterial pathogens involved with food poisoning include *Shigella, Campylobacter, Listeria,* and *E. coli.* Waterborne diseases most commonly are caused by *Giardia lamblia* followed by *Campylobacter jejuni.* Although it appears that the incidence of waterborne disease has decreased in the United States, foodborne illness continues to be a major health concern *(17).*

The major reservoir for transmission of *Salmonella* is domestic livestock, especially chicken and eggs. Infection most commonly occurs in the summer and fall. Infection is most likely to occur in children under the age of 1 yr, followed by individuals younger than 20 yr and older than 70 yr of age *(17).* Immunosuppressed individuals are predisposed to progressive salmonellosis with bacteremia. Symptoms may range from one or two loose stools per day to a cholera-like illness with profuse diarrhea and severe dehydration. Symptoms usually develop within 8–48 h after ingestion of contaminated food and usually last 2–3 d.

In a healthy host with mild to moderate symptoms no medical treatment is necessary. Indications for therapy include immunocompromised states and elderly patients (Table 2). Carrier states should also be considered for therapy with ciprofloxacin or norfloxacin for 3 wk.

Outbreaks of *Salmonella* in the last decade have demonstrated bacterial strains that are resistant to ampicillin, chloramphenicol, and trimethoprim, leading to the increased use of fluoroquinolones for primary therapy *(20).* More recent reports have shown spread of quinolone-resistant bacteria from food animals to humans, associated with infections that are more difficult to treat. Restriction of the use of fluoroquinolones in food animals should be considered *(21).*

In the United States, *Staphylococcus aureus* is the second most common cause of foodborne illness after *Salmonella.* Contamination is more frequent in high-salt and high-sugar foods. Symptoms usually begin within 1–6 h after ingestion of contami-

nated food and usually last for 24–48 h. Patients present with nausea, vomiting, and abdominal cramps followed by diarrhea. Treatment is supportive only—no antibiotic therapy is indicated *(17)*.

Shigellosis is seen primarily in children between the ages of 2 and 5 yr old. It is transmitted primarily through a fecal–oral route. Infection with *Shigella* usually occurs within 36–72 h of ingestion of contaminated food. The presentation of shigellosis is biphasic, beginning with abdominal cramps and watery diarrhea that lasts for 2–3 d, followed by dysentery with tenesmus and small volume bloody stools. Diagnosis can be made by examination of stool specimen *(5,17,19)*. *Bacillus cereus* is a recognized cause of foodborne illness in the United States. Foods that are cooked slowly at low temperatures allowing bacteria to proliferate are the most common source of infection. Symptoms usually occur within 6–14 h of ingestion of the contaminated food and may persist up to 3 days. Abdominal cramps and diarrhea are the most common symptoms; however, vomiting may also occur *(17)*. Supportive care only is required.

Most outbreaks of *Clostridium* diarrhea occur during the winter and fall. Symptoms include pronounced abdominal cramping with watery diarrhea. Symptoms usually begin within 8–24 h after ingestion of contaminated food. The disease is self limited and recovery occurs within 24 h. A different clinical syndrome related to the production of toxins by *Clostridium perfringens* may cause necrotizing enterocolitis. Broad-spectrum antibiotics and immediate surgical evaluation and intervention should be performed. The morbidity and mortality rates associated with this type of illness are high *(17)*.

Campylobacter jejuni is the most commonly recognized cause of bacterial gastroenteritis in the United States and is seen most frequently in young children. It usually occurs within 24–72 h after ingestion of contaminated food or water and the mean duration of symptoms is 1 wk. Patients usually present with a prodrome of malaise, headache, and fever followed by periumbilical pain and profuse diarrhea. *Campylobacter jejuni* can be detected in the stool.

Listeria monocytogenes is an uncommon cause of foodborne infection. It usually affects immunocompromised individuals; unpasteurized milk is the most common mode of transmission. *Listeria* can cause severe illness including sepsis; therefore, early diagnosis and initiation of antibiotic therapy is warranted (Table 2).

Escherichia coli

Escherichia coli is a common organism that inhabits the gastrointestinal tract. Most species are not pathogenic; however, there are several distinct pathogens that have been associated with gastroenteritis. These include enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC), and enterohemorrhagic *E. coli* (EHEC).

Enterotoxigenic *E. coli* is the major cause of diarrhea in children in underdeveloped countries. It is found in both food and water. Watery diarrhea and crampy abdominal pain are the most common symptoms. The mean duration of disease is usually 3–5 d and is usually self limited; therefore medical therapy is not required. If symptoms are more severe, patients should be treated as for traveler's diarrhea *(19)*.

Enteropathogenic *E. coli* typically affects children under the age of 2 yr. Patients usually present with profuse, watery diarrhea. Treatment is supportive. Some individu-

als may develop chronic or protracted symptoms and antimicrobial therapy may be indicated. Enteroinvasive *E. coli* has been described primarily in large outbreaks of foodborne illness. Symptoms may be indistinguishable from *Shigella* infections, including diarrhea that contains mucus, blood, and pus. The mean duration of symptoms is 4 d; however, symptoms may continue for up to 12 days *(19).*

EHEC (*E. coli* 0157:H7 infection) is characterized by hemorrhagic colitis and bloody diarrhea. Infection most often occurs after ingestion of contaminated foods, such as ground beef or unpasteurized milk or apple cider. EHEC can be complicated by hemolytic uremic syndrome (HUS) as well as thrombotic thrombocytopenic purpura (TTP) and can result in a high mortality. The bacteria can be easily detected in the stool. Early antibiotic therapy may predispose the patient to the development of HUS *(19).* Therefore, patients should be treated with antibiotics only if symptoms are severe (Table 2). Reports of resistance to ciprofloxacin as well as amoxicillin, chloramphenicol, and trimethoprim/sulfamethoxazole exist. This should be considered in those individuals who fail to improve with conventional therapies; culture and sensitivity determinations are indicated in this setting *(23).*

Typhoid fever (enteric fever)

The hallmarks of typhoid fever are prolonged fever and bacteremia in the absence of vascular compromise. Transmission is fecal–oral and is primarily seen in foreign countries. Typhoid fever can result in a high mortality; therefore antibiotic therapy is warranted (Table 2).

Yersinia

Yersinia infection is seen primarily in children, although it may affect adults as well. Chocolate milk, ice cream, and tofu are the most common vehicles of transmission. Patients usually present with abdominal pain localized in the right lower quadrant, and diarrhea and symptoms may mimic acute appendicitis or Crohn's disease. Illness tends to be self limited although chronic diarrhea may persist for months. There is no evidence that therapy is indicated or alters the course of this self-limiting illness. In the setting of sepsis, however, antibiotic therapy is recommended *(19,22).*

Vibrio Species

Vibrio, Aeromonas, and *Plesiomonas* are members of the Vibrio family and are recognized to cause illness in humans. Cholera is the accepted prototype of enterotoxigenic diarrhea and is caused by *Vibrio cholera.* In the United States, cholera is endemic on the gulf coast of Louisiana and Texas. Patients present with vomiting and abdominal distension followed by large volume diarrhea of >1 L/h. Dehydration and shock often occur. Aggressive fluid and electrolyte replacement should be administered.

Tetracycline is the drug of choice and remains a highly efficacious form of therapy. Tetracycline-resistant cholera is uncommon; however, if present the fluoroquinolones should be used. Doxycycline, trimethoprim–sulfamethoxazole, or erythromycin may also be effective. Furazolidone should be used in pregnant women *(19).* The mainstay of therapy remains aggressive fluid and electrolyte replacement to overcome bowel losses. Octreotide, a somastatin analog, has been shown to reduce the duration and

Table 2
Treatment of Gastrointestinal Infections

Organism	Vector	Symptoms	Duration	First-Line Treatment	Alternative Treatment
Salmonella typhi	Domestic livestock, eggs	May range from one or two loose stools per day to severe diarrhea and dehydration	2–3 d	Healthy host-supportive care Immunocompromised host—TMP-SMZ DS b.i.d. × 10 d. Carrier state—treat for 3 wk	500 mg Ciprofloxacin b.i.d./400 mg norfloxacin b.i.d./300 mg ofloxtacin b.i.d. × 10 d
Shigella	Fecal–oral transmission	Abdominal cramps and diarrhea for 2–3 d, then tenesmus and small volume bloody stools	5–7 d	TMP-SMZ DS b.i.d. × 3 d	500 mg Ciprofloxacin b.i.d. × 3 d
Staphylococcus aureus	High-salt and high-sugar containing foods	Nausea, vomiting, abdominal cramps, & diarrhea	24–48 h	Supportive care	
Bacillus cereus	Slow-cooked foods at low temperature	Vomiting, abdominal cramps, and diarrhea	3 d	Supportive care	
Clostridium		Abdominal cramps, watery diarrhea *necrotizing enterocolitis	24 h	Supportive care	
Campylobacter jejuni	Poultry, unpasteurized milk	Headache, malaise, fever followed by periumbilical pain & profuse diarrhea	7 d	250 mg Erythromycin q.i.d. × 5 d	500 mg Ciprofloxacin b.i.d. × 5 d
Listeria monocytogenes	Unpasteurized milk	Systemic illness/sepsis usually seen in immunocompromised individuals		2.0 g Ampicillin i.v.q. 4 h /gentamicin 2 mg/kg loading dose i.v. then 1.7 mg/kg/d div q8 h PCN All – TMP-SMZ 20 mg (kg/d) div q 6–8 h) Tetracycline, chloramphenicol, erythromycin, & high dose PCN 6 may be used.	
Typhoid fever	Fecal–oral transmission	Fever, bacteremia		Ciprofloxacin 500 mg b.i.d. × 10 d or 2 g ceftriaxone i.v. qd × 5 d	Chloramphenicol or cefixime

(continued)

Table 2 (continued)

Organism	Vector	Symptoms	Duration	First-Line Treatment	Treatment
Vibrio species	Endemic on gulf coast of Louisiana & Texas	Vomiting, abdominal distension followed by large-volume diarrhea (cholera). Dehydration/shock may occur.		Aggressive fluid/electrolyte replacement.	500 mg Tetracycline q.i.d. 1.0 g Ciprofloxacin × 1 dose or norfloxacin 400 mg b.i.d. × 3 d Doxycycline, TMP-SMZ and erythromycin may also be used. Furazoledone should be used in pregnant women.
Yersinia	Chocolate milk, ice cream, tofu, pigs	RLQ abdominal pain & diarrhea		Self limited If sepsis—2 g ceftriaxone i.v. qd × 5 d	Tetracycline, TMP-SMZ Chloramphenicol may be used.
Aeromonas & *Plesiomonas*	Contaminated water or shellfish	Similar to cholera		TMP-SMZ DS b.i.d. × 5 d ciprofloxacin	
Enterotoxigenic *E. coli* (also traveler's diarrhea)	Contaminated food & water	Watery diarrhea, crampy abdominal pain	3–5 d	Supportive care if mild systems 500 mg Ciprofloxacin b.i.d./ 400 mg norfloxacin b.i.d. 300 mg ofloxacin b.i.d. × 3 d	250 mg Flagyl b.i.d. × 7 d
Enteropathogenic *E. coli*		Profuse watery diarrhea (age <2)	May develop chronic systems.	Supportive care If protracted symptoms: 100 mg/kg/d neomycin div q6h or 15 mg/kg/d colistin div q6h	TMP-SMZ DS b.i.d.
Enteroinvasive *E. coli*	Large outbreaks of foodborne illness	Fever, diarrhea with blood, mucus, pus (dysentery)	4 d (may go up to 12 d)	TMP-SMZ DS b.i.d. × 7 d	500 mg Ciprofloxacin b.i.d.
Enterohemorrhagic *E. coli*	Beef, unpasteurized milk	Bloody diarrhea (can develop Hemolytic Uremic Syndrome)	Variable	TMP-SMZ DS b.i.d.	500 mg ciprofloxacin b.i.d. 400 mg Norfloxacin b.i.d. 500 mg Amoxicillin q.i.d.

severity of diarrhea in the illness. However, large controlled trials are lacking to further support the use of octreotide in this setting *(24).*

Other Bacteria

Aeromonas hydrophilia and *Plesiomonas shigelloides* are other pathogens that can be acquired by consuming contaminated water or eating shellfish. Symptoms of these disorders are similar to those of cholera. Trimethoprim–sulfamethoxazole DS twice daily or ciprofloxacin is the treatment of choice.

Pseudomembranous Colitis (PMC)

Clostridium difficile is recognized as a common cause of nosocomial infection as well as the major cause of antibiotic associated colitis in the United States *(26).* Hospital outbreaks have been attributed to epidemic strains that are high toxin producers, although nontoxigenic strains are becoming increasingly recognized. *C. difficile* does not readily colonize the gastrointestinal tract of older adults and children unless those individuals have been treated with antibiotics, are undergoing cancer chemotherapy, or have infection with another pathogen such as *Salmonella* or *Shigella.* Another predisposing conditions for *C. difficile* infection may be underlying inflammatory bowel disease *(27).* Most patients with PMC present with diarrhea and crampy abdominal pain which typically begins within the first week of antibiotic therapy; however, PMC may occur up to 6 wk after antibiotic therapy has been completed. Some patients may complain of tenesmus, lower abdominal cramping, nausea, and occasional vomiting. Fever, chills, and dehydration may accompany severe colitis. Hematochezia is rarely observed.

The diagnosis of pseudomembranous colitis can be confirmed by sigmoidoscopy, which reveals small yellow-white plaques. Pseudomembranes may also be seen at the time of colonoscopy, giving the appearance of a white exudate covering the entire mucosa. *C. difficile* may also be detected by cytotoxin assay of the stool. Fulminant *C. difficile* colitis is rare; however, it may be severe enough to result in perforation of the bowel and peritonitis. Surgical intervention may be necessary in this setting *(27).*

Many individuals with *C. difficile* colitis will recover with discontinuation of the antibiotic therapy that is responsible for the colitis. However, because of significant morbidity and mortality in some patients with *C. difficile* colitis, most patients are treated with antibiotics. The recommended treatment of choice is 250 mg of metronidazole four times a day for 10 d. Oral vancomycin in a dose of 125 mg four times a day can also be used; however, it is more expensive than metronidazole and is not recommended as first-line therapy owing to concern about antibiotic use favoring selection of vancomycin-resistant organisms *(28).* Oral fusidic acid and oral teicoplanin are also both effective. In addition, 20,000 U of acetasone every 6 h may also be used. A different approach may be the use of nonpathogenic microorganisms that inhibit the growth of *C. difficile.* For example, *Saccharomyces boulardi* has also been shown to eradicate *C. difficile* from the stool *(29).*

About 15–20% of individuals who have been treated successfully will relapse after the initial course of therapy is stopped *(30).* The mechanism of relapse is unclear; however, antibiotic resistance does not appear to be a factor. Relapse is accompanied by moderate to severe symptoms. A second course of antibiotic therapy is indicated. In

this setting, a longer duration of therapy with metronidazole or vancomycin may be indicated. Rifampin in a dose of 600 mg b.i.d. for 7 d has been reported to cause eradication of *C. difficile* in patients with symptomatic relapse *(27).*

Recent reports have identified epidemics of PMC caused by a clindamycin-resistant strain of *C. difficile (31).* Resistance was attributable to the *ermB* gene, which encodes a 235 ribosomal RNA methylase that mediates resistance to macrolide lincosamide and streptogramin antibiotics. Restriction of clindamycin use was associated with resolution of the outbreaks.

Diverticulitis

Diverticulitis occurs when a diverticulum in the colon becomes inflamed or infected. Patients with early diverticulitis who have only mild symptoms may be mistakenly diagnosed as having only symptomatic diverticulosis. Symptoms of diverticulitis include abdominal pain, nausea, vomiting, fever, and localized abdominal tenderness with or without a mass effect. As the course progresses, manifestations may change. Late complications include abscess formation, free perforation, fistulization, or obstruction. The major organisms that appear to be pathogenic in the course of diverticulitis include anaerobes *(Bacteroides fragilis),* Gram-negative bacilli *(E. coli),* and Gram-positive coliforms *(Streptococcus fecalis) (32).*

The medical management of diverticulitis depends on the stage of the disease. For mild uncomplicated disease, oral trimethoprim–sulfamethoxazole and oral metronidazole may be adequate. Despite the development of new broad-spectrum antibiotics, the gold standard of treatment for more serious disease still remains triple therapy including intravenous ampicillin, intravenous gentamicin, and intravenous metronidazole or clindamycin. Cefoxitin has also shown to be as efficacious as gentamicin and clindamycin in the treatment of acute colonic diverticulitis. If symptoms are mild, single agents such as ampicillin–sulbactam, imipenem–cilastatin, or ticarcillin clavulanate may be used. Clindamycin appears to be an alternative to metronidazole and vancomycin may be substituted in penicillin-allergic patients. Antibiotics should be continued for 10 d *(32,33).*

Anal/Rectal Infections

Sexually transmitted enteric infections do occur in men who have sex with men, especially those who have multiple sexual partners. Women engaging in anal intercourse may also be at risk for these infections. These infections may be seen in healthy individuals as well as those who are immunocompromised such as with HIV infection. The pathogens most commonly associated with proctitis are *Neisseria gonorrhea, Chlamydia trachomatis,* HSV, and CMV. Other pathogens that may be isolated include *Giardia lamblia, Entamoeba histolytica, Shigella,* and *Campylobacter.* In these individuals stool studies as well as smears and culture for *Neisseria* should be performed. Flexible sigmoidoscopy may also be indicated. The approach to these disorders should be similar to that for disease in other areas of the GI tract.

Chronic Diarrhea

Chronic diarrheal illnesses that may be infectious in etiology include Whipple's disease and tropical sprue. Two other important diseases that may cause chronic diarrhea

are tuberculosis and histoplasmosis and treatment of these illnesses should be the same as that for systemic disease.

Parasites

Entamoeba histolytica is the cause of amebiasis. Infection is due to ingestion of fecally contaminated material. *E. histolytica* may invade the colonic mucosa to cause colitis or may travel through the portal vein to cause liver abscess. Most patients are asymptomatic; however, others will present with abdominal cramps and bloody diarrhea. Symptoms may become chronic and mimic ulcerative colitis. Diagnosis is made by examination of at least three stools for ova and parasites *(34).* A dose of metronidazole 750 mg three times a day for 5–10 d plus 650 mg of diiodohydroxyquin three times a day for 20 d is the treatment of choice. Paromomycin 500 mg t.i.d. for 10 d or 500 mg of diloxanide furoate t.i.d. for 10 d may also be used *(19).*

G. lamblia is the major cause of waterborne outbreaks of diarrhea in the United States. Person-to-person transmission is the second most common way of acquiring the disease. In children under the age of 3 yr in daycare centers, the prevalence of *Giardia* may be 20–50%. The most common symptom is diarrhea; however, malaise, abdominal cramps, nausea, and vomiting as well as weight loss may also occur in 60% of patients. Diagnosis can be made by detecting *Giardia* antigen in the stool. Endoscopy with duodenal aspirate and small bowel biopsy may also be useful *(34).* The treatment of choice is 100 mg of quinacrine three times a day for 5 d (no longer manufactured in the United States). Alternative treatment is 250 mg of metronidazole three times a day for 5–7 d 2 g of tinidazole in a single dose, or 400 mg of albendazole daily for 5 d. Patients with IgA or IgM deficiency should be treated for 6–8 wk. Paromomycin should be used if *Giardia* infection occurs in pregnant women *(19,34).*

In 1993, the cryptosporidiosis outbreak in Milwaukee was the largest waterborne outbreak ever noted in the United States *(25).* Large waterborne outbreaks have also occurred in England, Texas, Georgia, and Wisconsin, likely due to cattle contaminating nearby water supplies. Diarrhea typically lasts 10–14 d and may be accompanied by abdominal cramping, weight loss, and low-grade fever. In most healthy adults and children the disease is self limited. *Cryptosporidia* is also a well-recognized cause of severe diarrhea in patients with AIDS. In these patients, *Cryptosporidia* may cause a severe cholera-like illness. The diagnosis of cryptosporidiosis can be made by examination of stool for ova and parasites *(34).*

No effective therapy for cryptosporidiosis is available. Spiramycin, paromomycin, or azithromycin may be useful; however, data surrounding the use of these antibiotics is limited. If symptoms are severe, 500 mg of paramomycin t.i.d. for 7–14 d should be given *(19).* For treatment failures, azithromycin may be used.

Cyclospora, Isospora belli, and *Microsporidia* are other agents that may cause infectious diarrhea, especially in patients with AIDS. *Isopora belli* and *Cyclospora* can be eradicated with use of trimethoprim–sulfamethoxyzole DS b.i.d. for 7 d or pyrimethamine; however, no treatment is available for the Microsporidia *(19).*

HEPATITIS C

Hepatitis C is caused by an RNA virus that has many features similar to the flaviviruses *(35–39).* Hepatitis C represented 16% of the cases of acute hepatitis in the

sentinel study from the CDC from 1982 to 1993. Despite this, hepatitis C represents more than half of all the cases of chronic viral hepatitis in the United States. The incubation of the infection is from 2 to 26 wk. Clinical illness occurs in 30–40% of the patients, but only 20–30% of all the patients will develop jaundice.

There are an estimated 20,000 new cases of hepatitis C infections in the United States every year. Of these, 8400 are clinically apparent and very few will develop fulminant hepatitis. The overall prevalence of this infection in the United States is 1.8% with a total of 3.9–4 million persons in the United States suffering from chronic hepatitis C that will result in 8000–10,000 deaths every year.

The acquisition of hepatitis C is most often via the parenteral route, most commonly related to injected drug abuse. Other patients may acquire infection by transfusion or transplanted organs. Hemodialysis and accidental injuries with infected needles are other sources of infection. Additional risk factors include sexual contact with an infected person, nonparenteral cocaine abuse, multiple sex partners, or birth from a hepatitis C infected mother. The rate of transmission from monogamous heterosexual relations is in the order of 1.1–5.4%. Perinatal transmission from an infected mother who is HIV negative is approx 4.5% and for the mother who has coinfection with HIV it is approx 18%. The risk of a health care worker acquiring infection after percutaneous exposure with an infected needle is estimated to be 1.8% (range 0–7%) and only one case has been described secondary to a conjunctival splash.

In the United States, 38% of cases of hepatitis C have been related to use of intravenous drugs and 44% occur in patients of low socioeconomic status. However, in the "low socioeconomic group," more than 60% of infected individuals have used nonparenteral drugs, mostly cocaine by inhalation, and a fifth of them also have a history of sexually transmitted diseases. Sexual or household contact with a person infected with hepatitis C is found in only 10% of the cases, history of transfusions in 4%, occupational risks in 2%, and hemodialysis in 1%. Currently, 40% of the patients who have chronic liver disease have hepatitis C as a single or contributing factor. Approximately 26% have hepatitis C as the only factor and 14% have concomitant hepatitis C and alcohol abuse.

Many patients who have chronic hepatitis C infection are asymptomatic at the time that the diagnosis is established. Later, fatigue is the most common symptom and is found in 60% of the patients. Itching (30% of the patients) and abdominal pain (nearly 30%) are also frequent.

The progression of the hepatitis C tends to be very slow and may take 20, 30, or 40 yr to evolve from the time of acquisition to the development of complications from advanced liver disease. Eighty-five percent of patients infected with hepatitis C will develop chronic infection. Of those with chronic infection, perhaps 20% will evolve to cirrhosis (17% of the total). Of the cirrhotic patients, most remain well compensated over many years, but a subgroup will worsen and die of the disease (25% of cirrhotics or 4% of all the infected patients). These patients die either from complications of the chronic liver disease such as variceal bleed or spontaneous bacterial peritonitis or from hepatocellular carcinoma.

Alcohol is a critical cofactor for the development of hepatic injury in hepatitis C virus infected patients and as little as 10 g of alcohol a day increases the viral load. Amounts of alcohol in excess of 10 g a day cause additional elevation of liver enzymes with more accelerated progression of liver disease.

There are two approved therapies for chronic hepatitis C. One is interferon alone (Intron A, Roferon A, Infergen) and the second is a combination of interferon plus ribavirin (Rebetron). Patients who are most likely to receive benefit from therapy are those who show evidence of progression of disease. Liver biopsies are important to identify patients who have more advanced disease and differentiate them from those who have disease that is mild enough that it is not likely to progress. In the absence of "interface hepatitis" (piecemeal necrosis), fewer than 7% of the patients will develop cirrhosis over time. On the other hand, if interface hepatitis is present, even in the absence of fibrosis, the long-term risk of developing cirrhosis is 20–30%. Patients with more advanced disease with fibrosis outside the portal area, bridging inflammation, or necrosis have a chance of progressing to cirrhosis in the order of 70%.

Predictors of treatment outcome include viral load, genotype, and depending on the type of therapy, the presence or absence of cirrhosis. Patients with hepatitis C viral loads less than two million copies per milliliter tend to respond to therapy better. Patients with infection with genotype 2 or 3 respond better. In contrast, patients with genotype 1 (1a or 1b) or 4 tend to respond poorly. Other genotypes have been less studied. In therapies with a single agent (Interferon), the presence of cirrhosis also predicts poor response. Patients who have consistently normal liver enzymes over a period of 6 mo respond very poorly to therapy and should be treated only as part of study protocols.

Standard therapy with interferon alone is 3 million units three times a week for 12 mo. With that regimen, sustained virological response (absence of hepatitis C virus RNA 6 mo after therapy) is 13–19% (9% for genotype 1 and 30% for genotype 2 or 3). Similarly, patients with viral loads more than 2 million copies per milliliter have a sustained viral response (SVR) of only 10% compared with those who have <2 million copies per milliliter, who have a SVR of 30%. The presence of bridging fibrosis or cirrhosis also has a negative effect, with a SVR of 12% compared with 18% in the absence of fibrosis.

Combination therapy with oral ribavirin 1000–1200 mL a day depending on weight, plus 3 million units of interferon three times a week is more effective. The SVR to 48 wk of combination therapy is from 38% to 43% with a 1-yr course of therapy. SVR is only 31–35% for 6-mo therapy. In combination therapy, patients with hepatitis C due to genotype 1 respond less well (17% SVR with 6-mo therapy vs 29% SVR for 1-yr therapy). Genotypes 2 and 3 respond equally well to 6 or 12 mo of therapy with a SVR of 66%; clearly, these patients do not need a full year of therapy. Viral load also has some degree of importance and patients with more than 2 million copies per milliliter (Quantiplex test, Chiron Diagnostics) have a sustained virologic response of 38% compared with 45% for those who have <2 million copies. Patients with bridging fibrosis or cirrhosis have an SVR of 36% after 1 yr of therapy as compared with 43% in those without meaningful fibrosis. Patients with genotype 1, but with low viral load (< 2 million copies) have an SVR that is the same at either 6 or 12 mo of therapy (32%). Patients infected with genotype 2 or 3 have the same SVR with 6 or 12 mo of therapy, regardless of the viral load. The group that has been shown to obtain benefit from a full year of combination therapy is patients who have infection with genotype 1 (a or b) and viral load of more than 2 million copies, with sustained virologic response extending from 10% with 6 mo of therapy to 27% after 12 mo.

Patients who responded to interferon therapy and then relapsed after discontinuation or by the end of follow-up can be treated with reasonable success. There are two good therapeutic options: (1) Interferon alfacon-1 (Infergen) at a dose of 15 μg three times a week has been shown to give an SVR of 58% after 48 wk of therapy. (2) Rebetron (3 million units of interferon three times a week + 1000–1200 mg of ribavirin every day according to weight) gives an SVR of 46% after 24 wk of therapy. Here, there is also a difference in patients with genotype 1 who had an SVR rate of 29% as compared to the non-genotype 1 who had an SVR of 74%. Patients with high viral loads of more than 2 million copies per milliliter had an SVR of 42% as compared with those with lesser viral loads who had an SVR of 67%. In this case, the presence of cirrhosis did not make a difference in SVR (46 vs 49%).

HEPATITIS B

Hepatitis B is produced by a DNA virus classified as a hepadnavirus type 1 *(40–42).* There are multiple serotypes. More than 300 million people suffer from chronic hepatitis B virus (HBV) infection; more than 75% of affected individuals live in Asia or are of Asian origin. The usual incubation period is 2–3 mo but may be as short as 45 d and as long as 6 mo. The frequency of clinical illness with jaundice is different at different ages. Fewer than 10% of the patients acquiring infection when younger than 5 yr of age develop jaundice, while 30–50% of those older than 5 yr of age develop this clinical sign. The death rate associated with acute HBV infection is low, from 0.5% to 1.0%, and the rate of chronic infection is quite variable depending on the age at acquisition. For example, more than 90% of neonates infected with HBV will develop chronic infection and a carrier state, compared with 50% of infants, 10% of children older than 5 yr of age, and < 5% of adults. If patients develop chronic liver disease from HBV, 15–25% will suffer early mortality.

In the United States in 1989, 83% of acute HBV infections occurred in adults, 8% in adolescents, 4% in children 1–10 yr of age, and 4% in the perinatal period. However, the age distribution of chronic HBV is quite different; 24% of patients acquired the infection in the perinatal period and 12% at 1–10 yr of age. Adult and adolescent acquisition are less represented in the chronic infection group as compared with the frequency of acute infection, with 59% of chronic HBV cases having adult acquisition and 6% acquiring the infection during adolescence.

Concentration of HBV is very high in blood, serum, and wound exudates, and is moderate in semen, vaginal fluid, and saliva. Because of its concentration in genital fluids, HBV is classified as a sexually transmitted disease; sexual transmission is highly efficient. Levels of the virus are very low in urine, stools, breast milk, tears, and sweat. The most common routes of acquisition of infection are sexual, parenteral, and vertical (perinatal from mother to child). The risk factors for acquisition of acute HBV are heterosexual activity in 41%, intravenous drug abuse in 15%, homosexual activity in 9%, household contact in 2%, health care employment in 1%, and unknown source of infection in 31% of infected subjects.

Four percent of the acute HBV infections are due to vertical transmission from mother to child in the perinatal period. The highest risk of transmission is when the mother has hepatitis B e-antigen-positive markers. In this scenario, infection of the child will occur in nearly 90% of the cases. On the other hand, when the mother is

hepatitis B e-antigen-negative, the risk of transmission is closer to 15%. Depending on the age at acquisition of the infection (except in infants and toddlers), the most likely scenario is for the hepatitis B infection to be cleared with good recovery.

Patients who are chronically infected may be carriers and suffer almost no hepatic injury with minimal or nonexistent (nonreplicative phase) viral replication. Alternatively, they may have a more intense chronic hepatitis. Patients who are chronically infected and who have ongoing viral replication with elevated liver enzymes are at higher risk for progressive liver disease, and once cirrhosis develops, have a high risk for hepatocellular carcinoma. The development of cirrhosis, however, is not a prerequisite for the development of hepatocellular carcinoma.

The best marker for acute HBV infection is the hepatitis B core IgM antibody, which should always be present at the time the patient has evidence of clinical disease. For chronic infection (6 mo or longer) the most reliable marker is the presence of HBV surface antigen. It is very important to assess the degree of viral replication in chronic HBV cases, and this is usually determined by monitoring the evolution of liver enzymes, mostly alanine aminotransferase (ALT), and, most importantly, be determinations of HBV-DNA concentrations in serum by hybridization (quantitative) assays. The presence of hepatitis B e-antigen is less reliable because patients may have mutant strains of the virus and be hepatitis B e-antigen-negative, even during periods of active viral replication.

Interferon has traditionally been used as the treatment for HBV. The patients who have a better chance of response to this drug are those with well-compensated liver disease, moderately elevated liver enzymes (ALT of > 100), and only moderate elevation of HBV-DNA (< 200 pg/mL). Meta-analysis of the efficacy of interferon has shown that 33% of the patients who have chronic hepatitis B with significant viral replication may clear the hepatitis B e-antigen as compared with only 12% of the untreated controls. When treating hepatitis B, interferon is usually utilized at a dose of either 5 million units every day or 10 million units three times a week for a total of 16–24 wk. This form of therapy can be given only to patients who have no cirrhosis or who have very well compensated chronic hepatitis B with cirrhosis (bilirubin <3, absence of ascites, no previous varices bleed, serum albumin >3, and absence of hepatic encephalopathy). Interferon response, defined as loss of HB e-antigen and HBV-DNA (by hybridization or signal amplification quantitation) with normalization or near normalization of ALT where all are measured 6 mo after the end of therapy, occurs in 33% of the patients (vs 12% in controls). Loss of HBsAg occurs in 7.8% of the patients (vs 1.8% in controls).

The most recent addition to the armament against this virus is lamivudine (Epivir-HBV) at an oral dose of 100 mg a day. When Epivir-HBV was given for 52 wk to patients with chronic HBV, 15–17% of the patients responded by losing hepatitis B e-antigen, by developing hepatitis B e-antibody and by having nondetectable levels of HBV-DNA. This compared to a response rate of only 4–6% for patients receiving placebo. Importantly, when histological response was evaluated at the end of therapy, improvement was seen in 55–56% of the patients on lamivudine as compared with only 25–26% of the patients who were on placebo. Overall, the side effects of the drug were quite low and quite similar to those seen during placebo therapy.

One of the problems with lamivudine is risk of development of resistance, manifested clinically by elevation of HBV-DNA levels in all patients and elevation of ALT

in 50% of patients. The resistance mutation occurs in the YMDD locus of the virus and reduces the sensitivity of the virus to lamivudine. This resistance pattern is observed in 14% of the patients receiving this drug for 1 yr. Of importance, however, histologic improvements usually are maintained in spite of the mutation, probably because the mutant virus is less aggressive. Patients who develop lamivudine resistance could be considered for therapy with adefovir dipivoxil or with lobucavir, but the clinical experience with these drugs is very limited.

Current data suggest that long-term therapy with lamivudine is feasible but further study is needed. Patients on lamivudine therapy should be monitored at a minimum with monthly blood chemistries and with determinations of HBV-DNA quantitation at least every other month, but earlier if ALT rises. After discontinuation of lamivudine, patients should be followed with at least monthly determinations of ALT, HBV-DNA quantitation, hepatitis B e-antigen and anti-hepatitis B-e; if the disease reactivates, therapy should be restarted.

In the long term, the most effective way to prevent the occurrence of this disease is vaccination against HBV infection. Currently, vaccination is being offered to all neonates and now is starting to be given to preadolescent children and adolescents through age 18 ("catch up" vaccination). In addition to this, all health care workers and other groups at high risk should be vaccinated.

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is a frequent infection in patients who have cirrhotic ascites. The prevalence of SBP is 10–27% in patients hospitalized with ascites. Half of the cases of SBP will occur during a hospitalization course. The pathogenesis is probably related to transitory bacteremia, most often from the GI tract or urinary tract but also from skin, lungs, or after manipulation of the bowel in the case of endoscopy, or from transmural migration of bacteria, also known as intestinal translocation. The diagnosis is established by a polymorphonuclear cell count in ascitic fluid of >250 cells/mm^3 and is confirmed by a positive culture of ascitic fluid obtained at the bedside with direct inoculation of blood culture bottles. There is a subgroup of patients who fulfill the criteria of abnormal polymorphonuclear cell count but have a negative culture (culture-negative neutrocytic ascites), and this may represent just a false-negative culture. The behavior of patients with culture-negative neutrocytic ascites is quite similar to that of patients with SBP.

In SBP, a single organism is found in 90% of the cases and bacteremia is present in 40–60% of patients. The most common signs and symptoms include leukocytosis in 65–80% of patients, portal systemic encephalopathy in 50–70%, fever in 50–70%, abdominal pain in 50–70%, abdominal tenderness in 40–50%, and hypotension in 40%. Rebound is extremely unusual (<10%) because of lack of contact of visceral against parietal peritoneum. The most common organisms are Gram-negative bacilli which are responsible for 70% of the cases, including *E. coli* (43%), *Klebsiella pneumoniae* (8%), and others. The other important group of pathogens are Gram-positive cocci, representing 10–20% of the cases. Of these, the most common is *Streptococcus pneumoniae* in 8%, as well as α-hemolytic streptococcus and group D streptococcus in 5% each. *Enterococcus, Staphylococcus,* anaerobes, and microaerophilic organisms such as *Bacteroides, Clostridia,* and *Peptostreptococcus* are found in <2% of the cases.

If the fluid contains multiple bacteria, fungal elements, or anaerobic bacteria, a bowel perforation should be suspected. The sensitivity of ascitic fluid culture obtained by inoculating blood culture bottles at the bedside is 91%, while sending the fluid to the laboratory gives a sensitivity of only 42%.

The mortality of infection without therapy is high but not necessarily related to the SBP. Other complications including renal insufficiency and encephalopathy results in a 78–100% death rate without therapy and 30% with adequate therapy. The recurrence of infections after successful therapy is 69% at 1 yr. For that reason, control of ascites is critical to avoid new infections. In addition to this, prophylactic therapy should be given to patients who have ascites with a protein of <1.5 g/dL while they are hospitalized (usually with a quinolone, e.g., norfloxacin 400 mg a day, or with trimethoprim–sulfamethoxazole DS one tablet a day for 5 d of each week). After discharge from the hospital prophylaxis is a little more controversial but 500 mg of ciprofloxacin twice a day one day of each week may be adequate. No definite increase in resistant organisms has been documented in SBP patients receiving prophylactic antibiotics.

Therapy for SBP is usually 2 g of cefotaxime three times a day (corrected according to renal function) as initial empirical therapy. Therapy should be changed once susceptibility of the microorganisms is known. A length of therapy of 5 d seems to be adequate. Response to therapy may be assessed by a new paracentesis 48 h after the initiation of therapy with the expectation of finding a decrease in polymorphonuclear count to less than half of the original count. In general, use of aminoglycosides is avoided in patients with cirrhotic ascites because of the high nephrotoxicity and mortality associated with the use of these drugs.

Key Points

- Oral and esophageal candidiasis are important causes of disease in HIV patients, and the emergence of fluconazole resistance is a concern.
- *Helicobacter pylori* infection is now recognized as the cause of peptic ulcer disease and should be treated with antibiotics. A number of different regimes are effective but metronidazole and clarithromycin resistance are increasing.
- Infectious diarrheas cause a heavy burden of disease. Fluoroquinolones have become a treatment of choice for traveler's diarrhea owing to the emergence of resistance to the antibiotics traditionally used for this indication. Resistant *Salmonella* strains are a growing area of concern.
- *E. coli* 0157:H7 causes hemorrhagic colitis and may be complicated by hemolytic uremic syndrome. For severely ill patients, treatment should be guided by culture and susceptibility testing results, owing to the emergence of resistant strains.

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13
Endocarditis

Lena Daghestani

Infective endocarditis (IE) is an important cause of morbidity and mortality, and the incidence of this disease among the elderly, recipients of prosthetic valves, and intravenous drug abusers (IVDAs) has been increasing. The emergence of microbial resistance has complicated treatment of this disease. Primary prevention, early disease recognition, and prompt treatment are vital in reducing the incidence of IE as well as its complications *(1,2).*

CLINICAL DESCRIPTION

IE is described as acute or subacute and is further delineated as left-sided, right-sided, native valve, or prosthetic valve. These distinctions help clinicians determine the most likely pathogen and chose appropriate empiric therapy. Right-sided IE occurs in only 5–10% of patients. IVDAs compromise the majority of these patients, and the prevalence of disease in these patients is 30 times that of the general population. Interestingly, 5–10% of patients are not addicts *(2,3).* Hospitalization appears to increase the risk of right-sided IE among non-IVDA patients. Risk factors in this setting include intravenous and intracardiac catheterization, abdominal surgery, hyperalimentation, and indwelling pacemakers *(4–6).*

Left-sided IE occurs more frequently than right-sided IE. Patients typically have underlying cardiac abnormalities (acquired or congenital), prosthetic valves, poor dentition, and/or HIV infection. Dental, respiratory, genitourinary, or gastrointestinal procedures may also predispose high-risk patients (those with underlying valvular abnormalities). Infection with highly virulent organisms such as staphylococci and *Pseudomonas* spp. can cause IE in the absence of underlying risk factors or cardiac abnormalities *(2,3,7,8).*

The clinical presentations of IE are variable and depend upon the pathogen, the duration of infection, the heart valves affected, and the mode of disease acquisition. Clinical manifestations include bacteremia and systemic embolization. Vasculitis is a more prominent feature of subacute bacterial endocarditis (SBE) because immune complexes do not have time to form in acute IE *(1,9,10).* Fever is the most frequent finding in patients with IE, and this diagnosis should be entertained in patients with fever of unknown origin. It is noteworthy, however, that roughly 19% of patients with culture-negative IE are afebrile *(11).* Associated nonspecific symptoms of IE include

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weight loss, chills, night sweats, malaise, fatigue, nausea, cough, and arthralgias. Elderly patients may have few symptoms, and their ability to mount a febrile response may be blunted *(1,2,4,12,13).* Other clinical manifestations may include neurologic symptoms (stroke or focal deficits due to embolic phenomenon), mental status changes, subarachnoid hemorrhage (secondary to mycotic aneurysm rupture), splenomegaly (abscess or infarct), and flank tenderness (renal infarcts)*(1,2,12).*

A variety of cardiac complications may evolve in IE, including myocarditis, perivalvular abscess formation, mycotic aneurysm formation, and conduction defects. In addition, myocardial infarction may occur as a result of coronary artery embolism *(2,14).* The presence of new or changing insufficiency murmurs may also develop; however, their absence does not exclude the diagnosis of IE. Right-sided murmurs are rare and their presence should further heighten the suspicion of IE *(2,4,7,12,15).* Another important cardiac complication is congestive heart failure, frequently out of proportion to or in the absence of valvular abnormalities. This may be secondary to microbial antigenic mimicry resulting in the formation of antibodies directed against myocardial proteins *(16).*

The vasculitis observed in SBE is a consequence of immune complex formation and deposition. This occurs predominately in the kidney, spleen, and skin *(16).* The clinical presentation may be dominated by isolated immunologic phenomena without other signs and symptoms *(17).* Renal involvement can result in glomerulonephritis with subsequent hematuria, proteinuria, and urinary red cell casts *(1,4,12,16,18).* Cutaneous lesions including petechiae and splinter hemorrhages develop in as many as half of patients; however, these findings are neither sensitive nor specific for SBE. Osler's nodes—small, tender nodules found on the pads of the fingertips—are uncommon but may appear later in the course of the disease *(1,2,7,12,18).* Janeway lesions are non-tender macules that form on the fingers, palms, and soles. They are another uncommon cutaneous manifestation of IE that may result from systemic septic embolization or hypersensitivity angiitis *(2).*

Systemic embolization complicates the clinical picture in 22–50% of patients with IE *(9).* Patients with right-sided valvular vegetations may develop complications including pulmonary embolism, pneumonia, pulmonary hypertension, and lung abscess formation *(1,2,4).* In contrast, left-sided vegetations embolize to the major arterial beds in the central nervous system (CNS), heart, spleen, bowel, and extremities. This typically results in ischemia, infarction, hemorrhage, or abscess formation in the involved organ *(1,2,5,7,9,12,19).* Embolic events appear to be more common in left-sided IE and in IE caused by *S. aureus, Candida* spp., and the HACEK organisms *(7,9,20).*

Laboratory abnormalities frequently observed in patients with IE include an elevation in erythrocyte sedimentation rate, positive rheumatoid factor, cryoglobulinemia, leukocytosis, anemia, and elevations in blood urea nitrogen and creatinine *(1,4,7,16,17).* It is important to keep in mind that these abnormalities are not sensitive or specific in diagnosing IE, as they may also be present in a variety of other diseases.

The Duke criteria for the diagnosis of IE classify patients suspected of having IE into three categories based on the presence of specific pathologic and clinical criteria *(9,19)* (Table 1). Definite IE requires the culture or histological demonstration of microorganisms in a vegetation or intracardiac abscess or histological evidence of

Table 1
Duke's Clinical Criteria for Diagnosis of Infective Endocarditis

Major Criteria

Positive blood culture (no. 1 or 2)

1. Typical microorganisms consistent with IE from two separate blood cultures:
   a. *S. viridans, S. bovis,* or HACEK group, or
   b. Community-acquired *S. aureus* or enterococci in absence of primary focus
2. Microorganisms consistent with IE from persistently positive blood cultures:
   a. At least two positive cultures of blood samples drawn at least 12 h apart
   b. All of three or a majority of at least four separate blood cultures with first and last sample drawn at least 1 h apart

Evidence of endocardial involvement (no. 1 or 2)

1. Positive echocardiogram for IE defined as
   a. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
   b. Abscesses, or
   c. New partial dehiscence of prosthetic valve
2. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

1. *Predisposition:* IVDA or predisposing heart condition
2. *Fever:* temperature of at least 38° Centigrade
3. *Vascular phenomena:* major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. *Immunologic phenomena:* glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor
5. *Microbiological evidence:* positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
6. *Echocardiographic findings:* consistent with IE but do not meet a major criterion as noted above

Data from ref. *19.*

endocarditis in a vegetation or intracardiac abscess. In addition, the patient must manifest two major criteria, one major and three minor criteria, or five minor criteria (Table 1). When criteria for definite IE are lacking but the diagnosis cannot be rejected, the patient is considered to have possible IE. The diagnosis is rejected when there is a resolution of clinical manifestations within 4 d of antibiotics, when there is no pathological evidence of disease after at least 4 d of antibiotics, and when there is a firm alternate diagnosis to explain the symptoms *(19).*

Bacteremia is a major diagnostic criterion of IE; however, 1–5% of patients will have negative blood cultures. Culture-negative IE occurs predominately in patients infected with members of the HACEK group and in those with IE due to unusual organisms such as *Chlamydia* or fungi, as these microorganisms may often take weeks

to grow in culture with current techniques *(1,7,9,11,21).* Culture-negative IE may also result from the initiation of antimicrobial therapy prior to culturing the blood. In fact, administration of antibiotics prior to obtaining blood cultures may reduce bacterial recovery rate by 35–40% *(1,9,22).* Patients with culture-negative IE appear to have higher mortality rates, especially those with prosthetic valve endocarditis (PVE). This is presumably due to the delay in diagnosis and treatment *(7,23).*

Echocardiographic findings are also essential to the diagnosis of IE by the Duke criteria *(19).* Echocardiography has been particularly instrumental in the diagnosis of IE in patients with right-sided IE and culture-negative IE *(7).* Transthoracic echocardiography (TTE) has played an important diagnostic role in the initial management of patients suspected of having IE. It is rapid, noninvasive, and highly specific for detecting valvular vegetations *(24).* A major disadvantage of TTE is its low degree of sensitivity, and negative testing necessitates further imaging in patients strongly suspected of having IE. Furthermore, the ability of TTE to detect PVE and perivalvular abscess formation is limited. The usefulness of TTE is also limited in diagnosing IE in patients who have chronic obstructive pulmonary disease and in patients who are obese *(2,9,24).* Despite these shortcomings, a good quality TTE is still recommended as the initial procedure of choice for patients in whom the suspicion of IE is low *(9).*

Transesophageal echocardiography (TEE) has greater sensitivity than TTE, while maintaining a high degree of specificity, especially in patients with PVE *(1,2,7,9,20,24).* The most recent American Heart Association (AHA) guidelines recommend TEE as the procedure of choice in patients suspected of having PVE, for patients in whom the diagnosis of IE is intermediate or high, in patients who are difficult to image, and in patients with a high risk of complications *(9).*

Despite its high degree of sensitivity and specificity, TEE may be falsely negative in cases where vegetations are smaller than the limits of resolution, embolization of vegetations has occurred, or views are inadequate to detect small abscesses *(10,24).* Patients strongly suspected of having IE should undergo repeat TEE 7–10 d after an initially negative test *(9).* In patients who have undergone both TTE and TEE, the negative predictive value approximates 95% *(10).*

ETIOLOGY

The most commonly encountered pathogens in bacterial IE are streptococci, staphylococci, and enterococci. The HACEK organisms (*Hemophilus* spp., *Actinobacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.) and Gram-negative bacteria (*Klebsiella* spp., *Pseudomonas* spp., and *Esherichica* spp.) are less frequent offenders. Other rare but important pathogens include *Rickettsia* spp., *Bartonella* spp., *Legionella* spp., *Brucella* spp., *Neisseria* spp., *Mycobacterium* spp., fungi, and *Nocardia* spp. These unusual organisms as well as members of the HACEK group are responsible for the majority of culture-negative endocarditis *(1,7–9,25).*

Staphylococcus aureus is the predominant pathogen in right-sided IE, both in IVDA and other patients. *Candida* spp. have also been implicated as etiologic agents in both groups of patients. Gram-negative IE occurs more frequently in IVDA *(2,4,7,9).* In contrast, left-sided valvular structures are most often targeted by streptococci, especially *S. viridans. S. aureus* and enterococci are also frequently isolated pathogens. Enterococci are most likely among elderly patients *(1,2,7,8,12,19).*

PVE has become increasingly important owing to the increasing number of patients undergoing valve replacements. Of the roughly 50,000 patients receiving prosthetic valves annually, 1–6% ultimately develop IE *(1,9,26).* Early PVE, occurring within the first 60 d after valve replacement, is most often caused by staphylococci, predominately *S. epidermidis.* Mortality rates in early PVE range from 30% to 80%. Streptococci are the predominant infecting microorganisms in late PVE, with mortality rates ranging from 20% to 40% *(1,2,9,26,27).* The mortality rate of PVE is higher than that of native valve IE *(2,7,27).*

Two uncommon but important pathogens causing IE deserve special mention. *Streptococcus bovis* is predominately isolated in elderly patients with IE. Because of its tendency to form multiple, multivalvular vegetations, heart failure often develops, necessitating the need for extensive surgical repair. This results in higher mortality rates. Importantly, the presence of *S. bovis* mandates a complete examination of the upper and lower gastrointestinal (GI) tract due to its association with GI malignancy *(28,29). Staphylococcus lugdunensis* has recently emerged as an important cause of community-acquired IE in elderly patients. It is highly virulent and most often causes acute endocarditis. Metastatic seeding, perivalvular seeding with abscess formation, and rapid valve destruction frequently occur despite appropriate antibiotic therapy *(9,30).*

Recently, antibiotic-resistant microorganisms have emerged as an important cause of IE. The pathogens that have been particularly problematic are *S. aureus, S. pneumoniae, Enterococcus* spp., and *Candida* spp. Rates of penicillin resistant pneumococci have dramatically increased during the 1990s, and resistance levels of more than 40% are now reported in most regions of the United States *(31).* Although pneumococci are not a predominant cause of IE, mortality associated with infection is high *(32).*

The staphylococci developed early resistance to penicillin necessitating the use of penicillinase-resistant penicillins, that is, methicillin. The capacity of the staphylococci to elude eradication with even these drugs, however, has been steadily increasing. Methicillin-resistant *S. aureus* (MRSA) IE is most commonly seen in IVDA and in hospitalized patients, although some cases of community-acquired MRSA PVE have been reported *(33,34).*

The enterococci have long been an important cause of IE, and their susceptibility to the penicillins decreased many years ago. The increasing resistance of these organisms to aminoglycosides has compromised our ability to treat enterococcal infections; however, perhaps more concerning has been the emergence of vancomycin-resistant enterococci (VRE). The number of VRE infections, including IE, has been steadily increasing, and the lack of efficacious therapeutic alternatives has significantly hindered efforts to eradicate infection *(8,35).*

ANTIMICROBIAL THERAPY

Antibiotics for the treatment of IE should be bactericidal and directed against the microorganism cultured from the blood. IVDA and other patients with community-acquired infection may present with acute IE. In this setting, three blood cultures should be obtained as soon as possible (within 1 h of presentation), and empiric antibiotic therapy should be initiated immediately thereafter *(1,2).* Combined therapy with nafcillin and gentamicin is recommended in patients with acute IE because *S. aureus* is

the most common offending pathogen *(2).* Patients who are already on antibiotics, patients in whom infection with MRSA is suspected, patients with PVE (high likelihood of *S. epidermidis*), and patients with β-lactam allergy should be treated with vancomycin until antimicrobial sensitivities become available *(2).*

The treatment of SBE differs from that of acute IE in that antibiotic therapy can be delayed until after blood cultures have been obtained. Three sets of blood cultures (each set being one aerobic bottle plus one anaerobic bottle) should be obtained and each sample should contain at least 10 mL of serum. Collection should be from three different venipuncture sites and should be performed at least 1 h apart. With appropriate technique, blood cultures will reveal the offending pathogen in 95% of patients *(1,2,9,19).* Once the microorganism is identified, directed antibiotic therapy can be initiated. Table 2 summarizes the current regimens recommended for the treatment of native and prosthetic valve SBE.

ANTIMICROBIAL THERAPY OF RESISTANT ORGANISMS

Pneumococcus is an infrequent cause of IE; however, the mortality rate of disease approaches 60% *(32).* Penicillin was traditionally the antibiotic of choice, but the rapid emergence of drug resistance has necessitated the use of other antimicrobial agents. Unfortunately, many of the streptococcal strains isolated have also demonstrated resistance to the tetracyclines, macrolides, and sulfonamides. Consequently, the use of third-generation cephalosporins with or without vancomycin has been recommended as empiric therapy for pneumococcal IE. Once the organism and antibiotic susceptibilities are identified, therapy should be adjusted accordingly. The fourth-generation cephalosporins may have an increasingly important role owing to their enhanced activity against penicillin-resistant pneumococci. Optimal treatment is a combination of medical and surgical therapy *(31,32).*

The current drug of choice for the treatment of MRSA IE is vancomycin. The addition of rifampin and gentamicin is recommended for PVE. Despite susceptibility of staphylococci to vancomycin, failure with this therapy has occurred. In addition, relapse rates up to 15% following appropriate courses of therapy have been reported *(37).* Recent studies have demonstrated efficacy of the new fluoroquinolones, primarily levofloxacin and trovafloxacin, against experimental MRSA IE *(33,38–40).* These drugs have been shown to be superior to the earlier quinolones, that is, ciprofloxacin, and potentially more effective than vancomycin. In addition, the excellent bioavailability, penetration into and bactericidal effects on vegetations, clearance of bacteremia, and minimal development of resistance have made the newer quinolones attractive therapeutic potential alternatives *(33,38,39).* However, additional clinical trials will be needed before quinolones are considered an acceptable standard of care for MRSA IE.

Enterococci have become increasingly resistant to current therapy, and aminoglycoside adjuvant therapy is becoming less efficacious. Resistance to vancomycin has also emerged, particularly in nosocomial settings. The seriousness of this situation is compounded by the fact that no reliable, alternative treatment is currently available for patients with VRE IE. The use of third generation cephalosporins as well as previous vancomycin use predisposes patients to developing enterococcal infections, especially with VRE *(8,35).*

Table 2
Current Recommendations for Treatment of SBE

Microorganism	Primary Treatment	Alternative Treatment
Streptococci	PCN G (12–18 MU/d) × 4 wk	Ceftriaxone (2.0 g/d) × 4 wk
PCN-sensitive	OR	OR
Native valve and prosthetic valve	PCN G (12–18 MU/d) × 2 wk gentamicin (1 mg/kg/q8h) × 2 wk	Ceftriaxone (2.0 g/d) × 2 wk + gentamicin (1 mg/kg/q8h) × 2 wk OR Vancomycin (30 mg/kg/d) × 4 wk
PCN-resistant Native valve and prosthetic valve	PCN G (18 MU/d) × 4–6 wk + gentamicin (1 mg/kg/q8h) × 2 wk	Ampicillin 12 g/d for PCN OR Vancomycin (30 mg/kg/d) × 4 wk
Staphylococci		
Methicillin-sensitive Native valve	Nafcillin (12 g/d) × 4–6 wk + gentamicin (1.0 mg/kg/q8h) × 3–5 d OR Vancomycin (30 mg/kg/d) × 4 wk	Cefazolin (6.0 g/d) for nafcillin
IVDA	Nafcillin (12 g/d) × 2wk + gentamicin (1 mg/kg/q8h) × 2 wk	
Prosthetic valve	Nafcillin (12 g/d) × 6 wk + rifampin (900 mg/d) × 6 wk + gentamicin (1 mg/kg/q8h) × 2 wk	
Methicillin-resistant		
Native valve	Vancomycin (30 mg/kg/d) × 4–6 wk	
Prosthetic valve	Vancomycin (2 g/d) × 6 wk + rifampin (900 mg/d) × 6 wk + gentamicin (1 mg/kg/q8h) × 2 wk	
Enterococci (native and prosthetic valve)		
PCN-sensitive	PCN G (18–30 MU/d) × 8–12 wk	Ampicillin (12 g/d) instead of PCN
PCN-resistant	Unasyn (12.0 g/d) × 4–6 wk + gentamicin (1 mg/kg/q8h) × 4–6 wk	Vancomycin (30 mg/kg/d) instead of gentamicin
Vancomycin-resistant	No effective treatment	
HACEK group	Ceftriaxone (2.0 g/d) × 4 wk	Ampicillin (12 g/d) × 4 wk + gentamicin (1 mg/kg/q8h) × 4 wk
Native valve and prosthetic valve		

Data from refs. *1, 2, 8, 22, 36*

Patients with β-lactamase producing enterococcal IE should be treated with an aminoglycoside plus ampicillin–sulbactam or vancomycin. High-level aminoglycoside resistance, however, will preclude the bactericidal synergy of these agents, and surgical intervention is often necessary *(41)*. Anecdotal cases of successful treatment of patients with high-level gentamicin resistant enterococcal IE using ampicillin–fluoroquinolone combination therapy have been reported *(42)*.

Enterococcal infections resistant to vancomycin pose a serious therapeutic dilemma. Occasionally, patients may be infected with VRE that have low levels of resistance to ampicillin. These infections may be treated with very high dose ampicillin in combination with an aminoglycoside *(35)*. Strains of VRE with moderate resistance to β-lactams may be inhibited by the synergistic combination of these drugs with vancomycin and gentamicin. Success of this triple-drug regimen lies in the demonstration of β-lactam/vancomycin synergy, absence of high-level aminoglycoside resistance, and in vitro triple-drug bactericidal effects *(41)*. In the presence of VRE highly resistant to ampicillin, no reliable bactericidal regimen is currently available. The fluoroquinolones combined with β-lactams and/or aminoglycosides may have promise for treating strains of VRE lacking high-level fluoroquinolone resistance *(41)*.

In an attempt to prevent the ongoing emergence of VRE, guidelines outlining the appropriate use of vancomycin have been developed by the Hospital Infection Control practices Advisory Committee (HICPAC). Their recommendations deem vancomycin use appropriate in the following situations: (1) treatment of serious infections caused by β-lactam resistant Gram-positive bacteria; (2) treatment of serious infections with Gram-positive bacteria in patients with serious allergies to beta lactams; and (3) treatment of antibiotic-associated colitis when it is life-threatening or fails to respond to metronidazole. Importantly, vancomycin use is appropriate for the treatment of IE due to penicillin-resistant streptococci and MRSA and for IE in patients with serious penicillin allergies *(35)*. Health care providers have an obligation to both educate themselves regarding the appropriate use of antibiotics and to comply with current guidelines outlining the appropriate use of antimicrobial agents.

SURGICAL THERAPY

Surgery is an important adjunct to antibiotics in treating patients with IE. A primary indication for surgery is the presence of progressively worsening or refractory congestive heart failure (CHF). Valve replacement is recommended early in the course of CHF, as rates of morbidity and mortality are lower at this time. In fact, delaying valve replacement in CHF patients until severe ventricular dysfunction develops nearly doubles the rate of mortality *(1,9,43,44)*.

Combined medical and surgical treatment is clearly superior to medical treatment alone in patients with cardiac complications, PVE, and IE with resistant microorganisms. The role of valve replacement in patients with PVE who lack serious cardiac or CNS complications is not clearly defined, and some patients have been successfully treated only with antibiotics *(27,43,45)*. Factors which should be considered prior to valve replacement surgery include the patient's age and comorbidities, the type of prosthetic valve involved, and the expertise of the surgical team *(45)*.

The size of valvular vegetations and subsequent embolic phenomena are also important factors in determining the need for and timing of valve replacement. Typically, patients with small vegetations or asymptomatic aortic valve vegetations can be managed with medical therapy alone. If, however, the vegetations continue to increase in size despite appropriate medical treatment, valve replacement should be considered *(9,43).*

Embolic phenomena frequently occur when large, mobile valvular vegetations are present, and surgical repair should be considered. If embolic phenomena recur despite adequate antimicrobial therapy, valve replacement should be performed regardless of vegetation size. Valve replacement may also be employed in an attempt to prevent or reduce the number of embolic events. In this setting, surgery should be performed early in the course of IE when likelihood of systemic embolization is higher and in patients with other predictors of post-IE complications *(9,45).*

Other indications for which adjunctive surgery should be considered are: (1) progressive glomerulonephritis despite appropriate antimicrobials; (2) infection with highly virulent organisms; (3) perivalvular extension with or without abscess formation in patients with native valve IE; and (4) cardiovascular instability. In addition, surgery may be the only effective option in patients with IE due to resistant organisms for which medical therapy alone is limited *(1,9,27,33,43,44).*

ANTIMICROBIAL PROPHYLAXIS

Given the increasing incidence of IE among segments of the population, primary prevention is perhaps the most important aspect in reducing morbidity and mortality. Patient education and compliance are intrinsic to successful disease prevention. Although the incidence is low, IE following certain procedures can occur in some patients with underlying risk. Antimicrobial agents utilized prophylactically, in addition to other preventative measures, can reduce the risk of acquiring IE by 5–10% *(1,46).* In light of this, the AHA has established recommendations on the appropriate use of antibiotics for prophylaxis against procedure-related IE (Table 3).

In general, antibiotic prophylaxis is indicated in patients undergoing procedures involving the GI tract, the genitourinary (GU) tract, and the upper respiratory tract as well as in patients who undergo dental and oral procedures. *Enterococcus faecalis* is the most common cause of IE in patients undergoing GI or GU tract instrumentation, whereas *Streptococcus viridans* is the causative agent of procedure-related IE in the other aforementioned procedures *(46).*

Patients undergoing procedures likely to produce bacteremia are classified as having a high, moderate, or negligible risk of acquiring IE based on underlying cardiac conditions. Patients considered to be high-risk for developing procedure-related IE are those who have prosthetic heart valves, previous IE, congenital cyanotic cardiac abnormalities, and surgically constructed systemic pulmonary shunts. Moderate-risk patients include those with hypertrophic cardiomyopathy, acquired valvular dysfunction, and mitral valve prolapse with regurgitation or leaflet thickening. Antibiotic prophylaxis is recommended in both high- and moderate-risk patients. Patients with negligible-risk do not require antibiotic prophylaxis *(46).*

Table 3
AHA Guidelines for Prophylaxis of Infectious Endocarditis

Dental, oral, esophageal, and respiratory tract procedures

Patient	Drug of choice	Regimen	Alternative
Standard	Amoxicillin	2 g p.o. 1 h before	Ampicillin (2 g i.v. 30 min before)
PCN-allergic	Clindamycin	600 mg p.o. 1 h before	Cephalexin (2 g p.o. 1 h before) Azithromycin (500 mg p.o. 1 h before)

Genitourinary and gastrointestinal procedures

Patient	Drug of choice and regimen
High-risk	Ampicillin (2 g i.v.) + gentamicin (1.5 mg/kg i.v.) 30 min before and ampicillin (1 g i.v.)/amoxicillin (1 g p.o.) 6 h after
High-risk with PCN allergy	Vancomycin (1 g i.v. over 1–2 h) + gentamicin (1.5 mg/kg) within 30 min of procedure
Moderate-risk	Amoxicillin (2 g p.o.) 1 h before or ampicillin (50 mg/kg i.v.) 30 min before
Moderate-risk with PCN allergy	Vancomycin (1 g i.v. over 1–2 h) within 30 min of procedure

Data from ref. *46.*

New, alternative therapeutic regimens for the treatment of IE due to resistant organisms such as MRSA and VRE are obviously needed. One agent recently approved for treatment of MRSA and VRE IE is quinupristin–dalfopristin (Synercid®). This drug is a semisynthetic streptogramin whose two components are synergistically bactericidal against a variety of Gram-positive bacteria. Anecdotal cases have reported successful eradication of VRE IE with Synercid®, either alone or in combination with other antimicrobial agents *(47,48).* The treatment of MRSA IE in rabbits revealed efficacy equal to vancomycin with lower serum levels and easier penetration of cardiac vegetations *(49).*

LY333328, a glycopeptide antibiotic, has been shown to be as effective as vancomycin in the treatment of MRSA IE in animals. Lysostaphin is a peptidase produced by *S. simulans* which is also being evaluated for the treatment of MRSA IE. Lyphostatin, either alone or in combination with vancomycin, appears to be more effective than vancomycin monotherapy in animal models *(37).* Other experimental drugs which are being evaluated for the treatment for VRE IE include *N*-alkyl derivatives of LY264826 and the oxazolidinones *(41,55).*

FUNGAL ENDOCARDITIS

Fungal endocarditis (FE) is rare and predominately occurs in hospitalized patients, in immunocompromised patients, in patients with prosthetic valves, or IVDA *(50–53). Candida* spp. and *Aspergillus* spp. cause the majority of FE; however, other non-*albi-*

cans Candida, Cryptococcus spp., *Histoplasma* spp., and *Coccidiomyces* spp. may be etiologic *(51,53).* Despite available antifungal therapy, mortality remains between 56% and 94% *(51).* Factors predisposing patients to the development of FE include widespread and prolonged use of antibiotics, invasive diagnostic procedures, previous bacterial endocarditis (BE), chemotherapy, and open-heart surgery *(51–53).*

There are no characteristic clinical features of FE that aid in distinguishing it from BE. Fever, constitutional symptoms, splenomegaly, and neurological complications may be observed. Massive and fatal embolization to more deep-seated organs (i.e., brain, mesentary, and heart) occurs with greater frequency in FE, most likely as a consequence of the larger vegetation size. Blood cultures can be negative in up to 50% of patients, but echocardiography will often visualize the large vegetations which are usually left-sided and may be nonvalvular. Diagnosis is often made by biopsy or surgical removal of a systemic embolus *(50–52).*

The current recommendations for the treatment of FE are surgical replacement of the involved valves with adjunctive antifungal therapy *(50,52).* Amphotericin B (AmB) is the antifungal agent of first choice, and many advocate the concomitant use of flucytosine or rifampin as synergistic agents. Intravenous fluconazole is used infrequently because its activity is limited to *Candida* spp. The optimal dose of antifungal therapy and duration of treatment are not clearly defined. A dose of 1 mg/kg/d of AmB (2–3 g total) for at least 8 wk has been advocated; however, no randomized, controlled trials have been conducted to substantiate this. The liposomal form of AmB can be used in higher doses and appears to have less toxicity than the nonliposomal preparation *(50,52).*

Despite the inherent role of surgery in treating FE, additional foci of infection often persist resulting in reinfection of the newly implanted prosthetic valves. FE may reemerge several years after initial diagnosis and treatment, necessitating meticulous follow-up. Although not substantiated by randomized, controlled trials, some advocate the use of life-long antifungal prophylaxis to prevent recurrence of FE *(51–53).*

The problem of antimicrobial resistance is not unique to bacteria. Resistant fungal infections are also emerging, particularly among the *Candida* spp. Previous exposure to antifungal agents, that is, AmB and the azoles, appears to predispose patients to developing resistant FE, particularly fluconazole monotherapy and prophylaxis *(51,54).* Although *C. albicans* azole resistance occurs most often in late-stage AIDS patients with oropharyngeal candidiasis, the azole resistance of other *Candida* species *(C. glabrata* and *C. krusei)* is increasing as a result of widespread fluconazole use *(54).*

Fungal resistance to AmB is rare. It is interesting to note, however, that some patients with fluconazole susceptible *C. albicans* infections developed resistance not only to fluconazole and other azoles but to AmB after azole therapy as well. It has been postulated that exposure to fluconazole results in depletion of the fungal membrane ergosterol content resulting in resistance to AmB. However, there is ongoing debate regarding azole–polyene antagonism which may also play a role in the development of antifungal resistance *(54).* Several experimental antifungal agents are being examined for potential use in the treatment of FE. These include β1,3-glucan synthase inhibitors (echinocandin analogs), chitin synthase inhibitors (nikkomycins), pradimicin analogs, and the second-generation azole voriconazole *(51).*

Key Points

- IE caused by antibiotic resistant bacteria is increasing and therapy should always be guided by susceptibility testing of isolates.
- MRSA PVE should be treated with vancomycin + gentamicin + rifampin.
- Optimal treatment for VRE IE has not been defined; infectious disease consultation is recommended.
- Surgery has an important role in many cases of IE, especially those due to highly resistant bacteria or fungi.

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14
Infections of the Central Nervous System

Avi Nath and Joseph Berger

INTRODUCTION

Infections of the central nervous system (CNS) continue to be a major health social and economic toll on society due to the significant morbidity and mortality associated with these infections. Proper recognition and early treatment can have a significant impact on outcome of most of these infections. This chapter presents a syndrome-oriented clinical approach to a patient with CNS infection with an emphasis on antimicrobial therapy (*see* Table 1). Specifically, we focus on acute and chronic meningitis, acute and chronic encephalitis, and space-occupying lesion syndrome.

ACUTE MENINGITIS

The presentation is dramatic with clinical manifestations developing over only a few hours to days. High fever, headache, photophobia, stiff neck, and altered mental state are the typical presenting symptoms. Headache and vomiting due to raised intracranial pressure may be a presenting manifestation in young children. Infants, immune suppressed individuals, and the elderly may not develop neck stiffness and hence may lack the cardinal signs of meningeal irritation. Most often other clinical signs or specific predisposing conditions may be absent. However, if present, they may offer important diagnostic clues.

Etiology

The leading causes of acute meningitis are viruses and bacteria. The most dreaded of all is meningoccal meningitis. The presence of purpura or petechial rash on the trunk, lower extremities, mucous membranes including conjunctiva but absence in the nail beds is highly suggestive but not diagnostic of meningococcemia. Children with fulminant meningococcal septicemia may develop the Waterhouse–Friderichsen syndrome characterized by cardiovascular collapse associated with hypoadrenalism and disseminated intravascular coagulation.

The leading cause of acute bacterial meningitis is *H. influenza* in children; however, the incidence seems to be decreasing following the introduction of an effective vaccine. It is frequently associated with epiglotitis or otitis media. The most common cause of bacterial meningitis in adults is *Streptococcus pneumoniae.* Medical conditions commonly associated with pneumococcal meningitis include pneumonia, otitis media, head

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trauma associated with CSF leaks, and alcoholism. Pneumococci are also the most common cause of meningitis in children with sickle-cell anemia and other aspleenic states.

Listeria monoctyogenes is an important cause of neonatal meningitis and transmitted via the maternal genital tract. Diabetics, renal transplant patients, alcoholics, the elderly, and sometimes normal individuals may also develop *Listeria* meningitis by ingesting contaminated food. *Listeria* typically causes a rhombencephalitis affecting predominately the post-fossa structures. Patients with neutropenia are at particular risk for meningitis due to *Pseudomonas aeruginosa* and other enterobacteria. Because of their inability to mount an inflammatory response, these patients may have minimal meningeal response.

The most common cause of viral meningitis are enteroviruses followed by arboviruses. Establishing the exact viral etiology is of academic and epidemiological interest because no specific treatment is currently available for these viruses. The only exception is human immunodeficiency virus (HIV) infection which may present with an aseptic meningitis at the time of seroconversion.

Noninfectious causes of acute meningitis include systemic lupus erythematosus, rare reactions to nonsteroidal antiinflammatory drugs, and diseases of uncertain etiology such as Mollaret's meningitis (herpes virus-2 implicated in some cases) (1) and Behçet's syndrome. Additionally, Subarachnoid-hemorrhage and pituitary apoplexy may present as acute meningitis.

Laboratory Diagnosis

In a patient with suspected meningitis, there exists an urgency to establish the diagnosis by a CSF evaluation because it has been clearly shown that delay in treatment is the most critical factor in determining morbidity and mortality with bacterial meningitis. However, it has become common practice to obtain a computed to mography (CT) or magnetic resonance imaging (MRI) scan prior to performing a lumbar puncture even in the absence of focal neurological signs. Such a practice may be justified in situations where neuroimaging can be obtained immediately, the patient does not appear seriously ill, or if there is uncertainty about the neurological findings. However, in the absence of focal neurological signs and/or papilledema, a lumbar puncture can be safely performed without first obtaining a CT or MRI scan. Following the lumbar puncture, antimicrobial therapy should be started promptly pending results. Because antibiotics take about 24 h to sterilize the cerebrospinal fluid (CSF), lumbar puncture can be done after starting antibiotics within the same day.

In general viral meningitis causes a lymphocytosis in the CSF with a normal protein and glucose, while bacterial meningitis causes an elevation of the polymorphonuclear cells and protein but a decrease in glucose in the CSF. The presence of hemorrhage in the CSF may suggest HSV-1 meningoencephalitis. Exceptions to these CSF patterns include hypoglycorrhachia with some viruses and polymorphonuclear pleocytosis early in the course of viral meningitis.

Treatment of Bacterial Meningitis

Empirical Therapy of Community Acquired Bacterial Meningitis

The most common organism in nonneonates is *Streptococcus pneumoniae.* However, increasing strains are resistant to penicillin and some are resistant to third-generation cephalosporins. Cephalosporin-resistant strains are usually a problem in children and not

Table 1
Antimicrobial Therapy of CNS Bacterial Infections Based on Pathogen

Organism	Antibiotic	Comments
Streptococcus pneumoniae		
Sensitive to penicillin	Penicillin G	
Relatively resistant to penicillin	Ceftriaxone or cefotaxime	
Resistant to penicillin	Vancomycin plus cefotaxime or ceftriaxone + intraventricular vancomycin	
Neisseria meningitidis	Penicillin G or ampicillin	
Gram-negative bacilli (except *P. aeruginosa*)	Ceftriaxone or cefotraxime	
Pseudomanas aeruginosa	Ceftazidime	May add aminoglycoside in first week of treatment.
Listeria monocytogenes	Ampicillin	Cephalosporines are in active.
Staphylococci	Nafcillin	
Methicillin-resistant staphylococcus	Vancomycin	May add rifampicin.
Streptoccocus agalactiae	Ampicillin or penicillin	
Haemophilus influenzae	Cefotaxime or ceftriaxone	Increasingly strains are resistant to ampicillin or chloramphenicol or both.
Enterobacteriaceae	Cefotaxime or ceftriaxone	

adults *(2)*. Hence for relatively penicillin-resistant strains (minimal inhibitory concentration 0.1 to 1.0 μg/mL) a third-generation cephalosporin (cefotaxime or ceftriaxone) is the drug of choice. For highly penicillin-resistant strains or cephalosporin-resistant strains (minimal inhibitory concentration >2.0 μg/mL), vancomycin with or without rifampicin is the antibiotic of choice. See table 1 for recommended drug therapy for other organisms. Patients with neutropenia and meningitis should be treated with a third-generation cephalosporin (ceftazidime for *Pseudomonas*) and vancomycin *(3)*.

Adjunctive Steroid Therapy

The inflammatory process, although essential to control the infection, can also be detrimental to the host due to the release of neurotoxic cytokines. Several studies have confirmed the benefit of concomitant use of dexamethasone therapy in children (2 mo of age). The American Academy of Pediatrics recommends 0.6 mg/g/d in four divided dosages given intravenously for the first 4 d of antibiotic therapy. Current recommendation is to start the first dose of steroids 20 min before initiation of antibiotic therapy. The most serious side effect of dexamethasone therapy is gastrointestinal bleeding. For this reason, concomitant intravenous H2 antagonist is recommended. The greatest benefit of steroid therapy has been in the prevention of sensorineural hearing loss due to *H. influenzae* meningitis in children (reviewed in ref. *4*).

SUBACUTE OR CHRONIC MENINGITIS

Subacute or chronic meningitis is characterized by a gradual onset, often without any predisposing factor. These syndromes run their course over weeks, months or years. The clinical signs include headache, fever, stiff neck, and altered consciousness. Lower cranial nerve palsies may accompany basilar meningitis.

Etiology

Of the treatable conditions, crytococcosis and syphilis can be easily diagnosed on the basis of serology and antigen detection. Lyme disease *(Borrelia burgdorferi)* with nervous system involvement usually presents as a chronic meningitis and should be suspected if a combination of facial nerve palsy (often bilateral) and aseptic meningitis is present. Later in the course of the disease it may cause an encephalomyelitis, although several patterns of peripheral neuropathies, radiculopathy, and myositis have also been described. The characteristic skin lesion erythema chronicum migrans is often accompanied by secondary annular skin lesions. Other symptoms may include myalgias, arthralgias, dysesthesias, or abdominal pain. The causative spirochete, *Borrelia burgdorferi,* is transmitted by the bite of an infected Ixodes tick. Infection can spread hematogenously to, heart, nervous system, joints, and other organs (reviewed in ref. *5).*

Fungal meningitis occurs primarily in individuals with immunosuppression. *Cryptococcus neoformans* is the most common cause of meningitis in patients with human immunodeficiency virus (HIV) infection and in transplant patients. Other fungal infections that may occur in individuals with defects in cell-mediated immunity may include *Coccidioides immites* and histoplasmosis. Patients with granulocytopenia or a functional abnormality of granulocytes as is seen in diabetes mellitus are at risk of developing infections due to *Candida, Aspergillus fumigatus,* and Zygomycetes organisms (mucormycosis). *Candida* infections may also occur through central lines and in patients on broad-spectrum antibiotic therapy.

Tuberculous meningitis in HIV-infected patients is very similar to that in non-HIV-infected patients, except that the HIV-infected patients are more likely to have symptoms suggestive of extrameningeal tuberculosis. CNS tuberculosis can occur in the absence of pulmonary tuberculosis *(6).*

Treponema pallidum is a spirochete that causes syphilis. It is now recognized that CNS disease can occur through all stages of the infection. Although several well-characterized CNS syndromes have been described with *T. pallidum* they can be broadly classified into meningeal involvement (asymptomatic, subacute meningitis, meningovascular syphilis) that occurs early and is still common and parenchymal involvement (general paresis, tabes dorsalis, and gumma), which occurs several years after the primary infection and is rare. In contrast to the preantibiotic era, neurosyphilis today is identified in young patients most often with HIV coinfection, and early symptomatic syndromes and asymptomatic neurosyphilis are identified more frequently than late neurosyphilis syndromes *(7,8).*

Important noninfectious causes include sarcoidosis, systemic lupus erythematsous, vasculitides, carcinomatous meningitis, and Vogt–Koyanagi–Harada syndrome.

Laboratory Diagnosis

Fungal meningitis is commonly present in a state of immunosuppression which is also often associated with thrombocytopenia; hence platelet counts should be per-

formed prior to performing a lumbar puncture. If the platelet count is <50,000/mm^3, platelet transfusion is necessary. Neuroimaging (CT or MRI scan), preferably with contrast, should also be performed in these patients, as fungal meningitis is often associated with intracranial mass lesions. Fungi are typically difficult to isolate and culture from the CSF, because the infection occurs primarily in the basilar cisterns, and fungi are seldom present in the lumbar thecal sac where the lumbar puncture is performed. Hence large volumes (40–50 mL) of CSF are typically necessary for fungal cultures, and to improve the chances of finding the organism, the CSF from the later tubes should be used and it should be centrifuged and the pellet used for cultures and smears. If repeated cultures are negative and it remains essential to establish a diagnosis, a cisternal puncture may be considered. Biopsy of the basilar meninges may also be performed, but it carries a high morbidity rate. Biopsy of the cortical meninges is typically negative and hence not useful. For cryptococcus, antigen detection by latex agglutination is the most sensitive and specific test available. However, in HIV-infected patients, cryptococci may be detected by India ink in nearly 80% patients *(9)*.

In tuberculous meningitis, similar to other chronic meningitides, a lymphocytic pleocytosis is commonly seen in the CSF. However, early in the course of the illness (2–3 d) polymorphonuclear cells may be present which are replaced by lymphocytes *(10)*. Similarly, following initiation of antituberculous therapy polymorphonuclear cells may reappear in the CSF *(11)*. Because tuberculous meningitis is also a basilar meningitis, similar guidelines should be followed with regards to collection and processing of CSF as discussed previously. In addition, in some patients with tuberculous meningitis, owing to the large amount of protein present, a cobweb-like clot may appear on the surface of the fluid if kept undisturbed for a few hours. Tubercle bacilli get trapped in this proteinaceous material and can be identified by a acid-fast bacilli (AFB) smear. Alternatively, by adding 95% alcohol to the CSF the proteins can be precipitated and then examined. Smears are positive in approx 10–30% patients with tuberculous meningitis. Cultures require 3–6 wk and are positive in approx 75% patients. Polymerase chain reaction for *M. tuberculosis* may help establish the diagnosis early.

Two types of serological tests are available for diagnosing syphilis, broadly called tryponemal and nontreponemal tests. The tryponemal tests detect specific antibodies against *Tryponema pallidum* antigens and include the fluorescent treponemal antibody absorption test (FTA-ABS) and the microhemagglutination-T pallidum test (MHA-TP). The nontreponemal tests detect antibodies against lipid antigens on the membrane of *T. pallidum* and include the Veneral Disease Research Laboratory test (VDRL) and the rapid plasma reagin test (RPR). The treponemal tests become positive earlier in the course of infection and are more specific than the nontreponemal tests. A large number of conditions have been described in which false-positive syphilis serology may occur *(12)*. Most studies use a newly reactive positive CSF VDRL as a criteria for diagnosis of asymptomatic neurosyphilis. In two large prospective studies of CNS syphilis, CSF findings of patients with and without HIV infection were compared *(13)*. The frequency of isolation of *T. pallidum* was similar in both instances, the only difference being the presence of a slightly greater lymphocytosis in the HIV-infected patients.

For diagnosis of Lyme disease, positive or equivocal results on an enzyme-linked immunosorbent assay (ELISA), immunofluorescent assay (IFA), or immunodot assay requires supplemental testing with a Western blot assay. A negative result on the West-

ern blot or ELISA indicates that there is no serologic evidence of infection by *B. burgdorferi (14).*

Once polymerase chain reaction (PCR) techniques become available for clinical use, they will revolutionize the diagnosis of chronic meningitis, owing to their extreme sensitivity and rapidity with which the diagnosis can be established *(15,16).*

Treatment

For all types of fungal meningitis, intravenous amphotericin B is the treatment of choice. The major side effect of amphotericin B is renal impairment; hence renal functions should be monitored every other day for the first month and then weekly for the duration of therapy. Addition of flucytosine allows a dose reduction of amphotericin B and hence decreases the chance of developing nephrotoxicity. However, at serum concentrations >100 μg/mL bone marrow suppression may occur and therefore drug levels should be monitored regularly. The risk of bone marrow suppression should be carefully weighed in patients with acquired immunodeficiency syndrome (AIDS) who may be on other drugs with similar side effects. In patients with AIDS and fungal meningitis, maintenance therapy with fluconazole is necessary for life *(17).*

Coccidial Meningitis

Treatment requires the use of intravenous and intrathecal amphotericin B administered preferably by an Ommaya reservoir. It is recommended that treatment be continued for at least 1 yr after the CSF returns to normal. Intrathecal steroids may be used to decrease drug related inflammatory reaction.

Cryptococcal Meningitis

In non-AIDS patients a clinical trial that compared fluconazole to amphotericin B showed that treatment with fluconazole required 36% fewer days of hospitalization *(18).* In non-AIDS patients, a negative or low cryptococcal antigen titer suggests that the infection is adequately treated. However, in patients with AIDS, CSF cryptococcal antigen may remain positive despite adequate treatment owing to release of antigen from dead cells or slow clearing of the antigen from the CSF. Hence the clinical status is the best indicator for response to therapy and repeated CSF evaluations are not needed. Serum cryptococcal antigen titers are useful in patients on maintenance therapy. A rising titer indicates a relapse and requires confirmation with cultures. Prognostic factors in AIDS patients includes the titer of cryptococcal antigen in CSF, serum albumin level, and CD4 cell count, which together with dose of amphotericin B, have the strongest association with failure to achieve negative CSF cultures by d 14 *(19).*

Tuberculous Meningitis

Initiation of empiric chemotherapy should not await the results of CSF cultures *(20).* Isoniazid and pyrazinamide have excellent penetration of the blood–CSF and blood–brain barriers even under noninflamed conditions and hence form the backbone of all antituberculosis therapy. Treatment of tuberculous meningitis in non-AIDS patients should be initiated with isoniazid, rifampicin, and pyrazinamide. Pyridoxine is given to prevent isoniazid-induced peripheral neuropathy. If antimicrobial resistance is suspected, ethambutol may also be added. Once a clinical response is noted, pyrazinamide and ethambutol may be discontinued (usually after 2 mo of treatment). Isoniazid and rifampicin should be continued for 9–12 mo. In patients with HIV infection it

is recommended that treatment be initiated with four drugs: isoniazid; rifampicin; the third drug, which should be either ethambutol or pyrazinamide; to and the fourth drug, which should be streptomycin, rifabutin, or clofazimine. The recommended dosage for isoniazid is two to three times that of non-AIDS patients (i.e., 10–15 mg/kg/d). Hence these patients should be carefully monitored for the development of peripheral neuropathy. Ethambutol causes a dose-related optic neuropathy, while rifampicin, pyrazinamide, and isoniazid can be hepatotoxic. The American Academy of Pediatrics *(21)* recommends the use of isoniazid, rifampicin, pyrazinamide, and streptomycin for 2 mo followed by isoniazid and rifampicin for another 2 mo. They recommend that liver function be monitored for the first several months. The Academy also recommends that the use of corticosteroids be considered in this patient population. Dexamethasone (0.3–0.5 mg/kg/d) is to be given during the first week of therapy followed by prednisone staring at 2 mg/kg/d and gradually tapered over 3–4 wk. The steroids decrease cerebral edema and the inflammatory reaction *(22)*.

Neurosyphilis

Penicillin is the drug of choice for neurosyphilis treatment. However, the total dose, the most appropriate formulation, and the duration of therapy remain a subject of debate. The CDC recommends intravenous crystalline penicillin G, 12–24 million units daily in divided dosages at 4-h intervals for 10–14 d. Lower dosages do not provide adequate CSF levels of the drug. An alternative regimen is the use of procaine penicillin, 2.4 million units given intramuscularly daily, plus probenecid, 500 mg orally, four times daily for 10–14 d *(23)*. The interactions of HIV and syphilis are still not completely understood. However, patients with syphilis and HIV infection are at increased risk for treatment failure, so that higher dosages of penicillin given for 10–14 d offer no clear advantage over standard regimens *(24)*. Careful observation coupled with a low threshold for repeat CSF evaluation remains the recommended management strategy for these patients *(25)*. In patients allergic to penicillin, tetracyclines, chloramphenicol and ceftriaxone have been suggested based on case reports. Erythromycin frequently results in treatment failure.

Lyme Disease

Intravenous ceftriaxone or cefotaxime are the treatment of choice for nervous system involvement with Lyme disease due to their good CSF penetration and long half-life *(26,27)*. However controlled trials have shown that intravenous penicillin *(28)* and doxycycline may be just as effective *(29,30)*. Courses of therapy ranging from 10 to 21 d are supported by the available evidence, although the optimal duration of therapy is unknown *(31)*. Recently a vaccine has become available for human use for individuals at high risk *(32)*.

ACUTE ENCHEPHALITIS

When encephalitis exists, evidence of diffuse or, less commonly, focal brain dysfunction accompanies or overshadows signs of meningeal irritation. Patients characteristically exhibit altered attention and consciousness, ranging from confusion to lethargy or coma. Motor function may be abnormal, with weakness, altered tone, or incoordination, reflecting dysfunction of the cortex, basal ganglia, or cerebellum. Severe cases may cause difficult to control generalized or focal seizures. Some patients

exhibit adventitious movements including myoclonus or tremor. Acute viral encephalitis almost always is accompanied with a fever; however, hypothalamic involvement may lead to hyperthermia or hypothermia, autonomic dysfunction with vasomotor instability, or diabetes insipidus. Abnormalities of ocular motility, swallowing, or other cranial nerve functions are uncommon. Spinal cord infection is usually inconspicuous but can result in flaccid weakness, with acute loss of reflexes in the most severe cases. Focal symptoms other than seizures are usually minor and overshadowed by generalized brain dysfunction. Focal involvement of limbic structures is particularly characteristic of rabies encephalitis.

Etiology

Herpes simplex virus type 1 (HSV) encephalitis is the most common identified cause of severe, sporadic viral encephalitis in the United States, accounting for approx 20% of the reported cases of encephalitis. Although immunological mechanisms are important in HSV latency and its peripheral reactivation, the appearance of HSV encephalitis does not appear to be related to immunosuppression. However, individuals with impaired cell-mediated immunity may have a modified clinical expression of the illness.

Cytomegaloinclusion virus (CMV) results in significant neurological disability in the setting of immunosuppression, particularly AIDS. Besides the well-characterized CMV retinitis this organism characteristically causes a ventriculitis in AIDS patients. Cranial neuropathies, nystagmus, and progressive ventricular enlargement may accompany a CMV ventriculitis. Other features may suggest a brain stem encephalitis, including internuclear opthalmoplegia, cranial nerve palsies, gaze paresis, ataxia, and tetraparesis. Nearly all patients with CMV encephalitis have systemic CMV infection.

Rabies results in a devastating, and invariably fatal encephalitis *(33).* Viral transmission characteristically results from the bite of a rabid animal. The interval between the bite and the onset of disease in most cases is 1–2 mo. This delay affords an opportunity for prophylactic post-exposure immunization after the bite. Once virus enters peripheral and CNS pathways, immune defenses are unable to suppress further replication and spread of infection. Clinical rabies begins with a prodromal phase, that may include nonspecific symptoms of malaise, fever and headache, but also local symptoms related to the site of the original bite. Within a few days, the illness takes one of two forms—encephalitic *(furious)* or paralytic *(dumb)* rabies depending on the source and strain of the infecting virus. In its initial phase, encephalitic rabies is often distinguished from other viral infections by irritability of the patient and hyperactive automatic reflexes. Hydrophobia with reflexive intense contraction of the diaphragm and accessory respiratory and other muscles is induced upon attempts to drink or even by the sight of water. Similarly, blowing or fanning air on the chest may induce intense laryngeal, pharyngeal, or other muscle spasms (aerophobia). High fever persists throughout the illness. Patients may also have spontaneously occurring inspiratory spasms and autonomic dysfunction (hypersalivation, nonreactive pupils, and piloerection). Seizures are rare. Paralytic rabies is less common and easily misdiagnosed. Weakness begins in the bitten extremity and spreads to involve all four limbs and the facial muscles early in the course. Helpful signs include myoedema and piloerection. Fever is also present. As the disease progresses, it may converge with the encephalitic

form accompanied by some of the same irritative phenomena. Both forms evolve into lethargy and coma with prominent alterations of respiratory and cardiovascular function. Tachycardia may precede bradycardia with ectopic rhythms and the breathing pattern becomes irregular with cluster or periodic respirations. Patients succumb to respiratory failure or cardiovascular collapse within a mean interval of 4–7 d from onset. Intensive supportive care may extend survival in rare cases.

Laboratory Diagnosis

Neuroimaging with head CT scanning or cranial MRI is generally regarded as the initial diagnostic measure when evaluating patient suspected of encephalitis. The MRI is significantly more sensitive and often reveals highly characteristic abnormalities, including the virtually pathognomonic increased signal abnormalities on T2 weighted sequences in the medial temporal, insular cortical regions, and inferior frontal cingulate gyri in patients with HSV encephalitis. These lesions are often bilateral. Heavy sedation or even general anesthesia may sometimes be required to perform the MRI due to agitation and poor level of cooperation for the study. The MRI is also sensitive in suggesting some of the other pathologies, such as, brain abscess, vasculitis, or demyelination, which may present in a similar fashion. Brain biopsy is rarely necessary for patients with herpes encephalitis owing to the benign nature of the treatment and the morbidity associated with the procedure. CSF PCR tests for HSV have a high specificity and sensitivity *(34,35)*. Yet, in an occasional patient it may be necessary to confirm the diagnosis if the focal encepalitis cannot be differentiated from a mass lesion. Necrosis with petechial hemorrhage is often so intense that the disease was once called acute necrotizing encephalitis. Microscopically, hemorrhagic necrosis with mononuclear inflammation characterizes involved areas, with neurons and glia often containing Cowdry type A intranuclear inclusions during the acute phase of infection. Perivascular cuffing, neuronophagia, and diffuse microglial hyperplasia are observed. Although gray matter is predominantly affected, the infection extends into the white matter as well. In addition to the necrosis and inflammation of the neural tissues, leptomeningeal infiltration by lymphocytes, plasma cells, and large mononuclear cells is also seen. In the immunosuppressed host, the inflammatory infiltrate may not appear as intense *(36)*.

In patients with CMV encephalitis, MRI may show ependymal or meningeal enhancement may be observed as well as areas of focal infarction or necrosis may be visualized. Progressive ventricular enlargement may suggest CMV ventriculitis. A prominent pleocytosis with polymorphonuclear leukocytes may occur in patients with CMV ventriculitis. This is a unique finding since all other viral CNS infections cause a lymphocytosis in the CSF *(37)*.

Rabies is usually suspected on the basis of a history of animal bite or other exposure. Although in as many as one third of cases no such history is obtained. Definitive antemortem diagnosis is established by immunohistochemical identification of rabies virus antigen in hair follicle nerve endings of biopsied skin, usually obtained from the nape of the neck or from corneal impressions. Postmortem diagnosis is usually made by histologic or immunohistochemical examination of the brain. Specific findings include the presence of Negri bodies, eosinophilic neuronal intracytoplasmic inclusions composed of viral nucleoprotein *(33)*.

Treatment

Effective antiviral therapy is available against HSV, CMV, and varicella, the latter two cause encephalitis in immunocompromised patients only *(38).* In immunosuppressed patients, long-term therapy may be necessary. Treatment of acute viral encephalitis except herpes is directed at symptom relief, supportive care, and preventing and managing complications. Strict isolation is not essential, although when enteroviral infection is suspected, precautions in handling of stools and the practice of careful hand washing should be instituted. Persons with measles, chickenpox, rubella, or mumps virus infections should observe the usual precautions of isolation from susceptible individuals. Arboviruses are not characteristically spread from person to person because they require an intermediate insect vector.

HSV encephalitis should be considered a medical emergency in light of its characteristically aggressive course and antiviral therapy with intravenous acyclovir should be administered at the time the diagnosis is considered. Treatment is best rendered in an intensive care unit. If the presumptive diagnosis is not confirmed, acyclovir can be safely discontinued. Acyclovir is administered by intravenous infusion as 10 mg/kg given over at least 1-h period every 8 h for 10 d. This agent selectively interacts with two herpes virus coded enzymes, thymidine kinase and DNA polymerase, rendering it specific to the herpes viruses. Excretion is by the kidney and it should be administered cautiously in patients with impaired renal function. Toxicity is rare and includes phlebitis, skin rash, elevation of transaminases, and gastrointestinal disturbances. Neurotoxicity may be manifested by tremors, hallucinations, seizures, and altered consciousness.

In the case of possible exposure to a rabid animal, the decision for vaccination depends on the type of exposure: an open wound or disrupted mucous membrane exposed to saliva may warrant post-exposure prophylaxis, whereas contact of saliva with intact skin may not. Prompt local wound care should include thoroughly washing with soap and water, then iodine or 70% ethanol. In the absence of previous vaccination, both passive (rabies immune globulin of human origin) and active (diploid cell vaccines) immunizations are administered. Rabies immunoglobulin should be injected in and around the wound and should not be administered on the same limb where the vaccine is given. Tissue culture-derived vaccines have a low incidence of adverse reactions in contrast to earlier nerve tissue-derived vaccines *(39,40).*

CMV neurological complications should be treated with ganciclovir or foscarnet; however, the evidence of their efficacy in these conditions is chiefly limited to case reports and small series. The emergence of CMV strains resistant to both agents has been observed and CMV encephalitis has developed in the face of maintenance ganciclovir therapy for CMV retinitis.

SYMPTOMATIC MANAGEMENT OF ENCEPHALITIS

The headache and fever of meningitis can usually be managed with judicious doses of acetaminophen. Severe hyperthermia (>40°C) may require vigorous therapy, but mild temperature elevations may serve as a natural defense mechanism and are best left untreated.

Patients with severe encephalitis often become comatose. Because, however, some may achieve remarkable recovery, vigorous support and avoidance of complications

are essential. Meticulous care in an intensive care unit setting with respiratory and nutritional support is usually justified.

Although seizures sometimes complicate encephalitis, prophylactic anticonvulsants are not routinely recommended. If seizures develop, they can usually be managed with phenytoin and phenobarbital. If status epilepticus ensues, appropriate vigorous therapy should be instituted to prevent secondary brain injury and hypoxia. Similarly, secondary bacterial infections should be sought and promptly treated.

Steroids should probably generally be avoided in the treatment of encephalitis because of their inhibitory effects on host immune responses. However, in the presence of significant cerebral edema with impending brain herniation, high-dose corticosteroid therapy (4–6 mg of dexamethasone every 4–6 h) should be considered. Although there is a theoretical concern about the slowing of viral clearance in the face of corticosteroid therapy, treatment of the accompanying vasogenic edema is imperative.

Prognosis

The prognosis of encephalitis depends on its etiology. Arbovirus encephalitides have variable mortality rates. Eastern equine encephalitis has the highest mortality rate of all arboviruses while California virus has the least. The mortality rates for most viral encephalitides are greater in children under 4 yr of age and in the elderly. Nonfatal encephalitis caused by Eastern, Western, and St. Louis equine encephalitis viruses leaves a relatively high rate of neurologic sequelae. Encephalitis associated with mumps or LCM virus is rarely associated with death, and sequelae are infrequent. Hydrocephalus has been reported as a late sequela of mumps meningitis and encephalitis in children. In patients with herpes encephalitis the age of the patient and the level of consciousness at the time of institution of therapy are determinants of the outcome. The best survival is observed in young individuals (<30 yr old) with only lethargy at the time of the institution of antiviral therapy. Patients with minor neurologic deficits may survive without severe long-term sequelae and return to normal function if antiviral therapy is instituted early *(41).* Relapse has been observed in rare patients despite seemingly adequate antiviral treatment *(42).* This relapse usually occurs within a few weeks of the resolution of the initial the acute illness and often results in severe sequelae. The pathogenetic mechanisms for relapse are unknown.

CHRONIC ENCEPHALITIS

Most chronic encephalitis syndromes have characteristic neurological manifestations that help distinguish one another. Chronic encephalitis due to HIV infection commonly manifests as a dementing illness. These symptoms are usually recognized in the later stages of the illness when the CD4 counts are <100 cells/mm^3. The symptoms of HIV dementia affect three main categories: cognitive, motor, and behavioral. The primary cognitive symptom is forgetfulness, associated with impaired concentration and difficulty reading. Lower extremity weakness and impaired balance are among early motor signs. Other features include abnormal smooth ocular pursuit, postural tremor, impaired coordination, and increased motor tone. The most commonly observed behavioral symptoms are apathy and social withdrawal, which are often mistakenly diagnosed as depression. Occasionally organic psychosis, such as, acute mania may be a primary manifestation of HIV dementia.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that occurs in immunosuppressed patients and is caused by JC virus, a papovavirus widely distributed among in the human population. JC virus exhibits a neurotropism exclusive to glial cells. PML is most commonly seen in the AIDS population where approx 5% of all AIDS patients develop PML. The clinical hallmark of PML is the presence of focal neurological symptoms and signs progressive over a few weeks to months associated with radiographic evidence of white matter disease in the *absence* of mass effect.

Subacute sclerosing panencephalitis (SSPE) is caused by measles virus. It usually affects children. Patients usually have a history of measles rash at <2 yr of age, and it is speculated that such early host exposure allows emergence of persistent defective virus replication. Owing to effective vaccination strategy against measles virus, its incidence has markedly decreased in recent years. SSPE usually begins with cognitive and behavioral changes; progresses to include motor dysfunction with prominent myoclonus, choreoathetosis, dystonia, and rigidity. It usually causes a progressive deterioration over 1–3 yr to eventual rigid quadriparesis and a vegetative state.

Laboratory Diagnosis

In a patient who presents with a clinical picture of chronic encephalitis, it is important to exclude noninfectious causes of dementia and other neurodegenerative diseases (*see* Table 2). For example, there are no laboratory or neuroimaging study results that are specific for HIV dementia. The diagnosis is established by excluding other causes of dementia and encephalitis. CSF frequently shows an elevated total protein (usually <65 mg/dL), mild pleocytosis (<20 mononuclear cells/mm^3), increased total immunoglobulin fraction, and oligoclonal bands. Neuroimaging studies generally show a variable amount of cerebral atrophy, ventricular enlargement, and diffuse or multifocal white matter abnormalities. These findings are nonspecific.

In patients with PML, CT scan of the brain reveals hypodense lesions of the affected white matter that generally have a "scalloped" appearance as a result of the subcortical arcuate fibers lying directly beneath the cortex. MRI is the preferred neuroimaging modality. It shows a hyperintense lesion on T2 weighted images in the affected regions. Contrast enhancement is seen in approximately 5–10% of pathologically confirmed cases of with either brain imaging technique. The enhancement observed is typically faint and peripheral. Routine analysis of CSF is nondiagnostic. The CSF protein may be elevated and myelin basic protein may be detected. PCR for JC virus has a sensitivity of 43–92% and specificity of 92–100%. Positive and negative predictive values for CSF PCR for JC virus approach 90%. In the United States, PCR is thus now routinely being used to establish the diagnosis of PML *(43)*.

In SSPE, the electroencephalogram (EEG) shows periodic complexes with synchronous bursts of two or three slow waves per second, recurring at 5- to 8-s intervals in the myoclonic stage. CT or MRI scan of the brain shows generalized atrophy. The CSF protein, glucose, and cells are usually normal but is characterized by a high immunoglobulin concentration, oligoclonal bands, and abundant intrathecal synthesis of antibody to measles virus antigens. Serum measles antibody titers are also high. These findings are usually characteristic for diagnosis, but brain biopsy may be needed in atypical cases. Gray matter is most prominently involved. The distinct pathology of SSPE includes gliosis, loss of myelin, and perivascular infiltrates of lymphocytes and

Table 2
Treatable Noninfectious Causes to Be Considered in Chronic Encephalitis

Anxiety
Depression
Alcohol
Recreational drugs
Medication side effects and drug interactions
Metabolic encephalopathy
Hypothyroidism
Vitamin B_{12} deficiency

plasma cells in white and gray matter. Neuronal cell loss is noted in later stages of the illness. Intranuclear Cowdry type A inclusions containing viral nucleocapsids are present in both neurons and glia. Measles RNA can be detected in the brain by PCR.

Prognosis

Without treatment, HIV dementia is typically rapidly progressive, with a mean survival of about 6 mo, less than half the average survival of nondemented AIDS patients *(44).* Occasionally, patients may remain mildly demented and cognitively stable until death. This variablity is in part dependent upon the severity of immunedeficiency at the onset of dementia. Those with CD4 counts <100 cells/cu mm progress more rapidly. Survival of patients has improved since the introduction of highly active antiretroviral therapy (HAART).

PML usually progresses to death within a mean of 6 mo. In approx 9% of patients with AIDS-associated PML, survival may exceed 12 mo and often with partial or nearly complete clinical and radiographic recovery. Factors associated with a more benign course include having PML as the presenting manifestation of AIDS, high CD4 T-lymphocyte counts, and contrast enhancement of the lesions on radiographic studies *(45).*

Treatment

At this point, it is impossible to make definitive recommendations about the optimum antiretroviral therapy for HIV dementia. Stavudine (d4T) and abacavir appear to be a useful alternatives to include in a combination regimen for patients with dementia, based on their pharmacokinetic properties, tolerability, and b.i.d. dosing. New information is emerging that stavudine may have a role in treating neurological disease based on favorable pharmacokinetic studies demonstrating that CSF nucleoside reverse transcriptase inhibitor, nevirapine, achieves good CSF levels and may also be useful to include in ART regimens for patients with HIVD, based on accumulating clinical experience. The relative CSF penetration of the antiretroviral drugs is provided in Table 3.

Currently there is no effective therapy for PML. Cytosine arabinoside has been shown to inhibit JC viral replication in vitro; however, a randomized, double-blind trial with intrathecally and intravenously administration of the drug in patients with AIDS-associated PML demonstrated no benefit. Because of their antiviral activity, interferons

Table 3
Antiretroviral Drugs—Generic, Trade Names, and Characteristics

Generic Name	Drug Class	Abbreviation	Trade Name	Common Side Effects (Comments)	CSF Plasma Ratio
Zidovudine	Nucleoside RT inhibitor	AZT, ZDV	Retrovir	Bone marrow suppression, GI upset, headache, myopathy	0.3–1.3
Didanosine	Nucleoside RT inhibitor	ddI	Videx	Peripheral neuropathy, pancreatitis, diarrhea (take on empty stomach)	0.2
Zalcitabine	Nucleoside RT inhibitor	ddC	HIVID	Peripheral neuropathy, pancreatitis, oral ulcers	0.1–0.4
Stavudine	Nucleoside RT inhibitor	d4T	Zerit	Peripheral neuropathy	0.2
Lamivudine	Nucleoside RT inhibitor	3TC	Epivir	Anemia, GI upset	0.1
Abacavir	Nucleoside RT inhibitor	ABC	Ziagen	GI upset, hypersensitivity reaction	0.3
Adefovir	Nucleoside RT inhibitor	ADV	Preveon	GI upset, elevated transaminases, nephrotoxicity (must take with L-carnitine 500 mg/d)	
Nevirapine	Nonnucleoside RT inhibitor	NVP	Viramune	Rash	0.5
Delavirdine	Nonnucleoside RT inhibitor	DLV	Rescriptor	Rash	<0.05
Efavirenz	Nonnucleoside RT inhibitor	EFV	Sustiva	Dizziness, nightmares, “disconnectedness,” rash	<0.05
Saquinavir	Protease inhibitor	SQV	Invirase Fortovase	(Take with a fatty meal, or up to 2 h after meal)	<0.05
Indinavir	Protease inhibitor	IDV	Crixivan	Kidney stones, hyperbilirubinemia (take on an empty stomach)	<0.05
Ritonavir	Protease inhibitor	RTV	Norvir	GI upset, circumoral paresthesias, diarrhea, fatigue	<0.05
Nelfinavir	Protease inhibitor	NFV	Viracept	Diarrhea (take with food)	<undetectable
Amprenavir	Protease inhibitor	141W94	Agenerase	Rash, headache, GI upset	<0.05

have been proposed as potential therapeutic agents in the treatment of PML and one retrospective study appears to demonstrate improved survival among persons receiving interferon α. However, its efficacy remains to be established. Since the introduction of highly active antiretroviral therapy, survival in AIDS-associated PML has appeared to improve *(43).* There is no established treatment for SSPE although case reports suggest that interferon with inosiplex may stabilize symptoms in some patients *(46).*

SPACE-OCCUPYING LESION SYNDROME

Cerebral abscesses result in focal neurological deficits depending on the site of the lesion. This include visual field deficits, focal seizures, aphasias, hemiparesis or hemisensory deficits, cranial nerve palsies, or cerebellar dysfunction. Nonfocal symptoms, such as a confusional state or personality disorder, may be an initial manifestation, but as the disease progresses focal symptoms eventually appear. If multiple cerebral abscesses are present, multifocal symptoms may result.

Etiology

Although a number of bacterial, fungal, and parasitic infections may cause cerebral abscesses, this section discusses primarily the management of cerebral toxoplasmosis, which since the emergence of HIV infection has become the commonest cause of cerebral abscess seen. The causative agent of toxoplasmosis is a coccidian parasite, *Toxoplasma gondii.* Cats serve as natural reservoirs of *Toxoplasma,* virtually any animal that ingests material contaminated with oocyts can become infected. The frequency and prevalence of *Toxoplama* infection in humans varies considerably depending upon age dietary habits, climate, and proximity to cats. *Toxoplasma* cerebral abscesses occur most frequently in patients with HIV infection. The clinical manifestations typically evolve over several weeks, and focal signs referable to the site of the abscess are noted. Interestingly, in this patient population, toxoplasma has a predilection to localize in the basal ganglia, not infrequently resulting in movement disorders such as hemichorea, hemiballism, Parkinsonism, or a rubral tremor *(47).* In fact, to date all patients with AIDS and hemiballism/chorea have been proven to have cerebral toxoplasmosis *(47).*

Diagnosis

In an immunosuppressed patient who presents with focal neurological signs and multiple cerebral ring enhancing lesions on neuroimaging, cerebral toxoplasmosis would be the most likely diagnosis. In fact, this presentation is so characteristic that current guidelines suggest that all such patients be treated with anti-*Toxoplasma* medications. A lack of response to such therapy should alert the clinician about the possibility of other conditions such as CNS lymphoma or progressive multifocal leokuencephalopathy. Rarely, cerebral infarcts, varicella zoster infection, and other bacterial and parasitic infections may mimic such a clinical presentation. In patients with solitary lesions, the possibility of cerebral lymphoma would be more likely. In patients who are seronegative for toxoplasmosis or are on prophylactic therapy for toxoplasmosis other diagnoses should be considered *(48).*

PCR for toxoplasma on CSF has a 100% specificity for documented or presumed encephalitis with a sensitivity of about 50%. Thus PCR on CSF is a useful diagnostic

tool, if a positive result occurs *(49).* Neuroimaging techniques demonstrate the abscesses usually as multiple ringenhancing lesions with mass effect and surrounding edema. They may be seen in the corticomedullary junction and in patients with AIDS the lesions frequent the basal ganglia *(47).* MRI is more sensitive than CT scan in demonstrating these lesions and T2-weighted hyperintensity correlates with necrotizing encephalitis and T2-weighted isointensity with organizing abscesses *(50).* Response to empirical therapy may also be used diagnostically. Nearly 90% of patients will respond clinically and radiologically to drug therapy for cerebral toxoplasmosis by 14 d of treatment. In patients who fail drug therapy for toxoplasmosis and in some patients with solitary lesions, biopsy of the lesion may be necessary to establish the diagnosis by the demonstration of tachyzoites

Treatment

The choice of drugs for treating cerebral toxoplasmosis is limited *(51).* There are only three drugs available and, of these, pyrimethamine and sulfonamide are invariably used in combination. Clindamycin is an alternative choice. Another drug, spiramycin, although effective against *Toxoplasma,* has poor CNS penetration but achieves high concentrations in the placenta and is useful for treatment of toxoplasmosis during pregnancy. Because long-term maintenance therapy is a common practice, particularly in patients with AIDS, a wider choice of antibiotics is urgently necessary, owing to potential problems with drug resistance and side effects.

Key Points

- In a patient with suspected meningitis, it is important to quickly establish the diagnosis by a CSF evaluation. Delay in treatment is the most critical factor in determining morbidity and mortality with bacterial meningitis.
- Because fungal meningitis is commonly present in a state of immunosuppression which is also often associated with thrombocytopenia, platelet counts should be performed prior to performing a lumbar puncture.
- HSV encephalitis should be considered a medical emergency in light of its characteristically aggressive course, and antiviral therapy with intravenous acyclovir should be administered at the time the diagnosis is considered. Treatment is best rendered in an intensive care unit.
- Cerebral toxoplasmosis is the most likely diagnosis in immunosuppressed patients who present with focal neurological signs and multiple cerebral ring enhancing lesions on neuroimaging.

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15
Common Infections of the Skin and Bone

Peter J. Carek and Jonathan Sack

INTRODUCTION

Common skin infections include impetigo, cellulitis, erysipelas, folliculitis, furuncles, and carbuncles *(1,2).* In addition, skin infections are commonly associated with animal and human bites *(3).* When necessary, subsequent antibiotic selection should be based on culture results and associated antibiotic sensitivity testing. This chapter provides an overview of the bacterial causes (*see* Table 1) and recommended initial antibiotic management of common skin infections, particularly in relation to current knowledge regarding antibiotic resistance.

IMPETIGO

Clinical Presentation

Impetigo is a skin infection commonly found in children of preschool age, but may also occur in adults. Impetigo accounts for about 10% of all pediatric skin problems *(4).* It typically spreads from one part of the body to another through scratching and is a highly communicable disease.

Impetigo has two classic forms: nonbullous and bullous. The nonbullous form is more common and accounts for approx 70% of cases. This form is commonly associated with a "honey-colored" crusted discharge. As intact skin is resistant to this form of infection, lesion of nonbullous impetigo commonly begin on the skin of the face or extremities following even minor trauma. Common lesions that precede nonbullous impetigo include chickenpox, insect bites, abrasions, lacerations, and burns. The differential diagnosis of nonbullous impetigo includes viral, fungal, and parasitic infections.

Bullous impetigo, a disease of mainly infants and young children, may appear purulent and, when the blister is removed, the area resembles scalded skin. Flaccid, transparent bullae develop most commonly on skin of the face, buttocks, trunk, perineum, and extremities. These skin lesions may have associated adenopathy, leukocytosis, and pruritus with no or minimal systemic symptoms or signs. Lesions are associated with little or no pain or surrounding erythema.

The clinical presentation of impetigo evolves in an orderly fashion from a small vesicle or pustule, which progresses into a honey-colored crusted plague *(1).* Lesions usually are <2 cm in diameter. In general, lesions produce minimal symptoms. Associ-

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Table 1
Bacterial Causes of Common Skin and Skin Structure Infections

Lesion	Commonly Associated Bacteria
Impetigo	
Nonbullous	*Streptococcus pyogenes* and/or *Staphylococcus aureus*
Bullous	
Cellulitis/erysipelas	*Streptococcus pyogenes*
	Staphylococcus aureus
Folliculitis/furunculosis/carbuncle	*Staphylococcus aureus*
Animal bites	
Cats	*Pasteurella multocida* subsp. *multocida* and *septica*
Dog	*Pasteurella canis*
	Staphylococcus aureus
Humans	*Bacteroides* spp.
	Eikenella comodens
	Fusobacteria
	Peptostreptococcus
	Staphylococcus aureus

Data from ref. *54.*

ated findings include lymphandenopathy and leukocytosis. Lesions usually resolve in 2–3 wk without treatment and do not generally leave a scar.

Epidemiology

Impetigo is predominately found in preschool-aged children. It is a highly contagious disease and often results in outbreaks.

Etiology

Previously, impetiginous lesions were primarily of streptococcal origin. Currently, most cases of impetigo in the United States involve *Staphylococcus aureus* or a combination of *S. aureus* and streptococci *(5).* Bullous impetigo is most always caused by coagulase-positive *S. aureus,* although it has been found to be caused by 8-hemolytic streptococci Group A *(6).*

Treatment

Untreated impetigo may take several weeks to resolve, with spreading and development of new lesions during the resolution period. Scarring rarely occurs.

This infection may be treated either with topical or systemic antiinfective agents (Table 2). The topical treatment of impetigo with mupirocin ointment has a response rate of 85–97% *(7,8).* Topical mupirocin is effective in 90% of cases and is more effective than oral erythromycin *(9).* Topical mupirocin has not been compared to commonly used oral antibiotics.

Impetigo may be treated systemically with an oral, semisynthetic penicillin that is penicillin resistant or a first-generation cephalosporin. Most clinicians recommend either dicloxacillin or cephalexin. The failure rate of erythromycin in the presence of resistant *S. aureus* is 47% *(9).*

Table 2
Recommended Initial Antibiotic Management for Common Skin Infections

Diagnosis	Antibiotic(s) of First Choice	Alternative Antibiotics
Impetigo—nonbullous	2% Mupirocin ointment three times daily 250–500 mg Cefalexin four times daily 250–500 mg Dicloxacillin four times daily	Erythromycin Azithromycin Clarithromycin Clindamycin
Impetigo—bullous	250–500 mg Cefalexin four times daily 250–500 mg Dicloxacillin four times daily	Erythromycin Azithromycin Clarithromycin Clindamycin
Cellulitis/erysipelas	Mild to moderate infection: 250–500 mg Cefalexin four times daily 250–500 mg Dicloxacillin four times daily	Erythromycin Azithromycin Clarithromycin Clindamycin
	Severe infection: 1.0–2.0 g Nafcillin i.v. every 4 h	Cephalospo in (second or third-generation) Ticarcillin–clavulinate Vancomycin
	Infections exposed to marine environment: 250–500 mg Tetracycline four times per day	Trimethoprim–sulfamethaxazole Ciprofloxacin
Periorbital cellulitis	500 mg Amoxicillin–clavulanate every 8 h or 40 mg/kg/d divided every 8 h	Azithromycin Clarithromycin Clindamycin
Perianal cellulitis	50 mg/kg/d Penicillin divided four times daily	Azithromycin Clarithromycin Clindamycin
Erysipelas	250–500 mg Cefalexin four times daily 250–500 mg Dicloxacillin four times daily	Erythromycin Azithromycin Clarithromycin Clindamycin
Folliculitis	250–500 mg Cefalexin every 6 h 250–500 mg Dicloxacillin four times daily	Erythromycin Azithromycin Clarithromycin Clindamycin
"Hot-tub folliculitis"	Conservative measures initially	750 mg Ciprofloxacin every 12 h
Furuncles/carbuncles	250–500 mg Cefalexin every 6 h 250–500 mg Dicloxacillin four times daily	Erythromycin Azithromycin Clarithromycin Clindamycin
Bites	500 mg Amoxicillin–clavulanate three times daily or 40 mg/kg/d divided every 8 h	100 mg Doxycycline every 12 h 1 g Ceftriaxone every 24 h

The nares and anogenital region are reservoirs for staphylococci in asymptomatic individuals. Intranasal application of mupirocin nasal ointment (5-d course) significantly reduces the incidence of skin infections in staphylococcal carriers with recurrent skin infections *(10)*.

CELLULITIS/ERYSIPELAS

Clinical Presentation

Cellulitis is an acute, spreading infection of the dermis that may involve the subcutaneous tissues and spaces *(1)*. As cellulitis is a relatively deep infection, skin breakdown often occurs. Hematogenous and lymphatic dissemination may occur as well. Patients usually present with an erythematous area of skin that is painful, warm and tender. Unlike erysipelas, the erythema associated with cellulitis does not have sharply demarcated borders. Lymphangitic streaking and lymphadenopathy are commonly present. Systemic symptoms, such as fever, chills, and general malaise, may also be present in severe cases.

Erysipelas (also known as St. Anthony's fire), a moderate to severe skin infection, is a superficial form of cellulitis that is manifested by well-demarcated edematous elevated borders. The face and scalp are the most commonly affected sites, followed by the hands and genitalia. Constitutional symptoms, such as malaise, fever, and chills, are often associated with this infection.

The diagnosis of cellulitis and erysipelas are both clinical. Needle aspiration, complete blood counts, cultures, and diagnostic imaging have been suggested to aid in the diagnosis. Blood cultures are not cost effective and are more frequently contaminated than positive in the evaluation of a patient with uncomplicated cellulitis *(11)*. In most cases, patient management does not change for bacteremic patients with uncomplicated cellulitis. When an unusual organism is suspected or the infection does not appear to be responding to appropriate antibiotic therapy for the suspected bacterial pathogen, a fine-needle aspiration with Gram stain and culture may provide additional assistance. Despite the marked inflammatory response, fewer than 30% of cases submitted to deep aspiration yield organisms *(12)*.

Specific forms of cellulitis related to the anatomical area of involvement also occur. Periorbital or preseptal cellulitis is an infection of young children. Inflammation of the lids and periorbital tissues without signs of true orbital involvement is present. This infection is often caused by direct trauma, an infected wound, or an abscess of the lid or periorbital region. It may be associated with respiratory infection or bacteremia. Periorbital cellulitis requires prompt treatment and careful monitoring so as to prevent spread of the infection into the orbit. Orbital or postseptal cellulitis is manifested by ocular findings of proptosis, chemosis, and decreased and painful extraocular movements *(13)*.

Perianal cellulitis is a superficial, painful eruption caused by Group A streptococci. This infection is often accompanied by itching or painful defecation *(14)*. This disorder is found almost exclusively in children. If the disorder becomes chronic, fissures, discharge, and rectal bleeding may occur.

Epidemiology

Cellulitis is often preceded by a history of inflammatory tinea pedis, stasis dermatitis, eczema, ulcers, puncture wounds, or other similar type skin lesions. Both cellulitis and

erysipelas are more likely to occur after minor trauma to the skin has occurred in an area where previous injury or disease has impaired the lymphatic or venous drainage.

Etiology

S. pyogenes and *S. aureus* are the major pathogens, but other streptococci, *Haemophilus influenza* type B, *Pseudomonas aeruginosa, Aeromonas hydrophila,* and *Vibrio* species can be involved. *Vibrio* species should be suspected if the cellulitis is associated with a wound that occurred while the patient was exposed to a marine environment. The aerobic and anaerobic microbiology of perianal cellulitis is diverse: *Peptostreptococcus* spp., *Escherichia coli,* and α-hemolytic streptococci (predominately *E. coli, Peptosreptococcus* spp., *S. aureus,* and *Bacteroides fragilis (15).* The majority of cultures obtained from peritonsillar cellulitis and abscess grew *Streptococcus pyogenes* group A *(16).*

The most common pathogen involved in erysipelas are β-hemolytic streptococci, although it may occasionally be caused by *S. aureus (17,18).*

Treatment

The treatment includes immobilization and elevation of the affected area, and antibiotics directed against the suspected organism *(19).* Severe cellulitis initially requires intravenous antibiotic therapy using a semisynthetic penicillin such as nafcillin. Alternatively, second- or third-generation cephalosporins, ticarcillin clavulante, or vancomycin may be used *(20).* Later, outpatient once-daily intravenous therapy may be employed, using long-acting cephalosporins such as ceftriaxone, or oral quinolones may be given.

Oral penicillinase-resistant penicillin or first-generation cephalosporins are commonly used in mild to moderate cases of cellulitis. Erythromycin, clarithromycin, azithromycin, and clindamycin are alternatives for treatment of mild cases *(21–23).* Erythromycin has been found to remain effective in the treatment of superficial skin infections in which was found erythromycin-resistant *S. aureus (24).* The role of fluroquinolones in the treatment of cellulitis is yet to be thoroughly studied. In a double-blind study *(25),* a 7-d course of levofloxicin was similar in efficacy to a 10-d regimen of ciprofloxacin. The clinical success rates for these antibiotics ranged from 93.5 to 97.8%. A tetracycline is recommended for cellulitis that is associated with a wound exposed to a marine environment.

Periorbital cellulitis may be treated with outpatient observation, local measures, and oral antibiotics, most commonly a combination β-lactam and β-lactamase-resistant drug or a second generation cephalosporin *(13).* Orbital cellulitis requires prompt hospitalization and ophthalmological evaluation.

Most patients with perianal cellulitis respond to oral penicillin (50 mg/kg × 10 d) or a combination regimen of oral penicillin and topical mupirocin *(14).*

FOLLICULITIS/FURUNCLES/CARBUNCLES

Clinical Presentation

Folliculitis is an infection of the pilosebaceous unit and involves only minor inflammation of an individual hair follicle. This infection is associated with minimal pain and surrounding erythema.

Gram-negative folliculitis most often develops as a superinfection in people who have undergone prolonged oral antibiotic therapy. It is characterized by pustules in the area of the nose. The pathogens in the superficial form of this infection are usually *Klebsiella* or *Enterobacter* species. A deep nodular or cystic form of Gram-negative folliculitis is caused by *Proteus* species and also tends to appear on the face.

Hot-tub folliculitis is a special form of Gram-negative folliculitis caused by *Pseudomonas.* It occurs within 6 h to 3 d after exposure to poorly maintained hot tubs. The trunk, buttocks, legs, and arms are sites of predilection. Mild constitutional symptoms, including fever and malaise, may accompany the cutaneous findings. Hot-tub folliculitis, which is generally a benign, self-limited condition, can progress to a serious illness in an immunocompromised host.

A furuncle is a deeper, more aggressive infection of a hair follicle or a cutaneous gland. These lesions range in size from 5 mm to 3 cm diameter and occur most commonly on hairy areas exposed to friction, trauma, or macerations (i.e., buttocks, face, neck, axillae, groin, thighs, upper back). Patients present with a painful, often fluctuant swelling. Pruritus, local tenderness, and erythema are often associated. As pus forms in the center of the lesion, the overlying skin becomes thin, the lesion becomes elevated, pain increases, and spontaneous drainage of pus ultimately occurs.

A carbuncle is a coalescent mass of deeply infected follicles or sebaceous glands with multiple interconnecting sinus tracts and cutaneous openings that drain pus ineffectively. Carbuncles usually occur in the thick skin on the back of the neck and the upper back. The lesions steadily worsen, with increasing pain, erythema, swelling, purulent drainage, and lateral enlargement. These lesions range from 3 to 10 cm in diameter. Fever and other systemic symptoms and signs are common.

Epidemiology

Hairy areas of the body, particularly the beard, scalp, back, legs, and arms, are common site of involvement. The patient may live in a warm, damp climate. Persons with diabetes are particularly susceptible to folliculitis. Other predisposing conditions include hot and humid weather, improper hygiene, tight clothing, occlusion caused by oil-based cosmetics or sunscreen products, and occupational exposure to irritating substances such as cooking oils, greases, or solvents.

Etiology

S. aureus cause most cases of folliculitis. *Micrococcus, Pityrosporum,* and *Demodex* organisms are organisms that normally colonize skin but may become pathogens in the immunocompromised patient *(26).* Gram-negative folliculitis is caused by *Klebsiella, Enterobacter,* and *Proteus* species and may occur as a superinfection in acne vulgaris patients treated with long-term antibiotic therapy *(27).* As previously noted, hot-tub folliculitis is a special form of folliculitis caused by *Pseudomonas aeruginosa.*

Treatment

Folliculitis is often treated with frequent use of soap and water and the application of topical antibiotic agents such as mupirocin, clindamycin, erythromycin, or bacitracin. Occasionally, the addition of a systemic antistaphylococcal agent is required. Furuncles and carbuncles often require incision and drainage. Along with mild cleans-

ing and warm compresses, antibiotic therapy should be attempted if the furuncle is not yet fluctuant, if there is evidence of surrounding cellulitis lymphadenitis, or if the lesion is on the face. Semisynthetic penicillins or first-generation cephalosporins are the drugs of choice.

BITES

Clinical Presentation

Each year, several million Americans mostly young children, are bitten by animals, resulting in visits to emergency departments, hospitalizations, and deaths *(28).* Ninety percent of these bites are from dogs and cats. Commonly, these bites develop an associated skin infection. Human bites are often more prone to infection and complications. The sequelae of animal or human bites include meningitis, endocarditis, septic arthritis, and septic shock. In addition, dog bites can result in crush injuries in addition to tears, avulsions, and punctures and cat teeth can easily penetrate the bones and joints of the hand.

Bite wounds become infected with the oral, salivary, or dental flora of the biting person or animal. These wounds may cause serious local or systemic infections. Successful outcomes depend on knowing the extent or depth of injury by selective surgical exploration, good wound care, including irrigation and elevation, appropriate antiinfectives, and minimizing the time interval from injury to treatment. In particular, bites involving the hand are potentially complex *(2).*

Epidemiology

Each year, several million Americans are bitten by animals, resulting in approx 30,000 visits to emergency departments, 10,000 hospitalizations, and 20 deaths, mostly young children *(28).* Ninety percent of these bites are from dogs and cats. Commonly, these bites develop an associated skin infection, with 3–18% of dog bites and 28–80% of cat bites becoming infected. Human bites are often more prone to infection and complications.

Etiology

Talan et al. *(28)* studied the infected wounds of 50 patients with dog bites and 57 patients with cat bites. Aerobes and anaerobes were isolated from 56% of the wounds, aerobes alone from 36%, and anaerobes alone from 1%; 7% of cultures had no growth. *Pasteurella* species were the most frequent isolates from both dog bites (50%) and cat bites (75%). *Pasteurella canis* was the most common isolate from dog bites and *Pasteurella multocida* subspecies *multocida* and *septica* were the most common isolated of cat bites.

Treatment

The initial management of bite wounds include irrigation, debridement, and cleansing. The approach to closure of bite wounds remains extremely controversial. In general, the chosen antibiotic should cover the oral flora of the animal, the skin flora of the victim, and any likely environmental contaminants *(3).* The initial antibiotic of choice is a combination β-lactam and β-lactamase-resistant drug (i.e., amoxicillin and clavulanic acid).

OSTEOMYELITIS

The term *acute osteomyelitis* is used clinically to signify a newly recognized bone infection. The relapse of a previously treated or an untreated, prolonged infection is considered a sign of chronic disease. Clinical signs persisting for more than 10 d correlate roughly with the development of necrotic bone and chronic osteomyelitis. Both acute and chronic osteomyelitis have been extensively reviewed recently *(29–32).*

Clinical Description

Acute osteomyelitis, predominately found in children, tends to have been seeded by a hematogenous route. The metaphysis of long bones is the most common location of osteomyelitis in children. Patients are usually seen within several days to 1 week of the onset of symptoms and present with signs of systemic illness as well as local signs. The diagnosis can be established if at least two of the following are present: (1) pus on aspiration, (2) positive bacterial culture from bone or blood, (3) presence of classic signs and symptoms of acute osteomyelitis, and (4) radiographic changes typical of osteomyelitis *(33).* Leukocytosis, elevation in the erythrocyte sedimentation rate, and C-reactive protein may be noted. Blood cultures are positive in 40–50% of patients with acute osteomyelitis. Typical findings in a child with acute hematogenous osteomyelitis include tenderness over the involved bone and decreased range of motion in adjacent joints. Plain radiographic evidence of bone destruction by osteomyelitis may not appear for approx 2 wk after the onset of a hematogenous bacterial infection. Magnetic resonance imaging (MRI) or bone scan can be helpful in unclear situations.

Osteomyelitis in adults is most often subacute or chronic and is usually secondary to an open wound. Open injuries to bone and surrounding soft tissue are the most common settings in which pyogenic osteomyelitis occurs in adults. The incidence of deep musculoskeletal infection from open fractures has been reported to be up to 23% *(34).* Host factors can increase the risk of osteomyelitis. Altered neutrophil defense, humoral immunity, and cell-mediated immunity increase the risk of osteomyelitis. The cardinal signs of osteomyelitis include draining sinus tracts, deformity, instability, previous surgical scars, local signs of impaired vascularity, range of motion, and neurological status. As the diagnosis of osteomyelitis is mainly based upon clinical findings, initial laboratory data serves primarily as a benchmark against which treatment response is measured. Plain radiographic evidence of bone destruction by osteomyelitis may not appear for approx 2 wk after the onset of a bacterial infection. In osteomyelitis of the extremities, radiography and bone scintigraphy remain the primary tools of investigation *(35).* For nuclear imaging, technetium Tc-99m methylene diphosphonate, a technetium phosphate compound, is still the radiopharmaceutical of choice *(36).* Ultrasound is a useful second line of investigation for identifying subperiosteol abscesses, soft tissue abscesses, and joint effusions. In difficult cases, MRI is uniquely informative in the diagnosis and site of infection. MRI is particularly appropriate when there is suspicion of osteomyelitis, discitis, or septic arthritis involving the axial skeleton and pelvis. MRI or bone scan can be helpful in unclear situations.

Osteomyelitis is classed by the Cierny–Mader classification (Table 3), which is determined by the status of the disease process regardless of its etiology, regionality, or chronicity. The anatomical types of osteomyelitis are medullary, superficial, localized,

Table 3
Cierny–Mader Staging System (1985)

Anatomical type
Stage 1: Medullary osteomyelitis
Stage 2: Superficial osteomyelitis
Stage 3: Localized osteomyelitis
Stage 4: Diffuse osteomyelitis
Physiological class
A host: Healthy host
B host: Systemic compromise (Bs)
Local compromise (B1)
Systemic and local compromise (B1s)
C host: Treatment worse than the disease
Systemic or local factors that affect immune surveillance, metabolism, and local vascularity
Systemic (Bs)
Malnutrition
Renal or hepatic failure
Diabetes mellitus
Chronic hypoxia
Immune disease
Malignancy
Extremes of age
Immunosuppression or immune deficiency
Local (B1)
Chronic lymphedema
Venous stasis
Major vessel compromise
Arteritis
Extensive scarring
Radiation fibrosis
Small vessel disease
Neuropathy
Tobacco abuse

and diffuse *(37).* Stage 1, or medullary osteomyelitis, denotes infection confined to the intramedullary surfaces of the bone. Hematogenous osteomyelitis and infected medullary rods are examples of this anatomical type. Stage 2, or superficial osteomyelitis, occurs when an exposed infected necrotic surface of bone lies at the base of a soft tissue wound. Stage 3, or localized osteomyelitis, is usually characterized by a full-thickness cortical sequestration which can be removed surgically without compromising bony stability. Stage 4, or diffuse osteomyelitis, is a through-and-through process that usually requires an intercalary resection of the bone to arrest the disease process.

The patient is classified as an A (healthy), B (compromised, either systemically and/or locally), or C (treatment worse than the disease) host. The terms acute and chronic are not used in this staging system as areas of macronecrosis must be removed

Table 4
Commonly Isolated Organisms in Osteomyelitis

Infant (<1 yr)	Child (1–16 yr)	Adult (>16 yr)
Group B streptococci	*Staphylococcus aureus*	*Staphylococcus aureus*
Staphylococcus aureus	*Streptococcus pyogenes*	*Staphylococcus epidermidis*
Escherichia coli	*Haemophilus influenzae*	*Pseudomonas aeruginosa*
		Serratia marcescens
		Escherichia coli

Data from ref. *29.*

regardless of the acuity or chronicity of an infection. The stages are dynamic and may be altered by successful therapy, host alteration, or treatment.

Epidemiology

Acute osteomyelitis develops after bacteremia mostly in children and in elderly patients *(38).* In children, infection is usually located in the metaphyseal area of long bones (particularly the tibia and femur), usually as a single focus. Osteomyelitis after injury is the most prevalent type found in adults and is usually associated with an open fracture or occurs after surgery necessary for reconstruction of bone. The incidence of deep musculoskeletal infection from open fractures has been reported to be up to 23% *(34).*

Etiology

The specific microorganism isolated from patients with bacterial osteomyelitis is often associated with the age of the host or a common clinical scenario (Tables 4 and 5). The gold standard for diagnosing osteomyelitis in histopathologic and microbiologic examination of bone. Sinus tract cultures are not a reliable source for causative organisms and biopsy advocated to identify the cause of osteomyelitis *(39).* This retrospective study was limited by a lack of uniform specimen collection and prior antibiotic use. *S. aureus* is the organism implicated in the vast majority of cases of acute hematogenous osteomyelitis, causing up to 90% of cases in otherwise health children *(40). S. aureus, S. epidermidis, Pseudomonas aeruginosa, Serratia marcescens,* and *Escherichia coli* are commonly found in chronic osteomyelitis.

Treatment

Early antibiotic treatment, before extensive destruction of bone or necrosis, produces the best results and must be administered parentally for at least 4, usually 6, wk to achieve an acceptable rate of cure (Table 6) *(38).* To reduce costs, parental administration of antibiotics on an outpatient basis has become widely used. Treatment includes evaluation, staging, establishing the microbial etiology and susceptibilities, antimicrobial therapy, dead-space management, and stabilization *(41).*

As reviewed by Haas *(42),* only five comparative studies involving 154 patients have been reported *(43–47).* Clinical studies delineating treatment for osteomyelitis are difficult for numerous reasons: debridement obscures the impact of antibiotics, clinical

Table 5
Microorganisms Isolated from Patients with Bacterial Osteomyelitis

Microorganism	Most Common Clinical Association
S. aureus of osteomyelitis	Most frequent microorganism in any type
Coagulase-negative staphylococci or propionibacterium	Foreign-body associated infection
Enterobacteriaceae or *Pseudomonas aeruginosa*	Common in nosocomial infection
Streptococci or anaerobic bacteria	Associated with bites, fist injury caused by contact with another person's mouth, diabetic foot lesions, decubitus ulcers
Salmonella or *Streptococcus pneumoniae*	Sickle-cell disease
Bartonella henselae	HIV
Pasteurella multocida or *Eikenella corredens*	Human or animal bites
Aspergillus, Mycobacterium avium complex, or *Candida albicans*	Immunocompromised host
Mycobacterium tuberculosis	Populations in which tuberculosis is prevalent
Brucella, Coxiella burnetti (chronic Q fever), or other fungi found in specific geographic areas	Population in which these pathogens are endemic

Data from ref. *38.*

situations and pathogens are heterogeneous, and years of follow-up are necessary to demonstrate sustained remission. Animal models of osteomyelitis have been developed to study the pathophysiology and to compare antimicrobial efficacy.

Acute hematogenous osteomyelitis is best managed by care evaluation of its microbial etiology, early surgical intervention in adults (usually not in children), and a 4–6-wk course of appropriate parenteral antimicrobial therapy. When this regimen fails, debridement (or repeated debridement) plus another 4–6-wk course of parental therapy are essential *(41,48,49).*

After cultures have been obtained, a parental antibiotic regimen is begun to cover clinically suspected organisms. Hematogenous osteomyeltis can usually be treated with antibiotics alone. Children should receive 2 wk of initial parenteral antibiotic therapy before changing to an oral agent *(50,51).*

Treatment of pediatric acute staphylococcal osteomyelitis has been simplifies using cephdrine 150 mg/kg/d divided four times daily or clindamycin 40 mg/kg/d divided four times daily *(33).* The treatment is initiated intravenously, but switched to oral administration within 4 d. The mean hospitalization was 11 d and the total duration of antimicrobials was 23 d. No failure occurred nor have long-term sequelae been observed.

Osteomyelitis in adults is more refractory to therapy and is usually treated with antibiotics and surgical debridement. Depending upon the type of osteomyelitis, the patient may be treated for 2–4 wk with parental antibiotics. Without adequate debridement, most antiobiotic regimens fail no matter what the duration of therapy. Outpatient

Table 6
Initial Antibiotic Regimens for Therapy of Osteomyelitis

Organism	Antibiotic(s) of First Choice	Alternative Antibiotics
Staphylococcus aureus or coagulase-negative (methicillin-sensitive)	2 g Nafcillin every 6 h or 900 mg clindamycin every 8 h	First-generation cephalosporin Vancomycin
Staphylococcus aureus or coagulase-negative (methicillin-resistant)	1 g Vancomycin every 12 h	Teicoplanin Sulfamethoxazole–trimethaprim Minocycline + rifampin
Various streptococci (Group A Or Group B 8-hemolytic) or penicillin-sensitive *Streptococcus pneumoniae)*	4 million units Penicillin G every 6 h	Clindamycin Erythromycin Vancomycin Ceftriaxone
Intermediate penicillin-resistant *Streptococcus pneumoniae*	1 g Cefotaxime every 6 h OR 2 g Ceftriaxone once a day	Erythromycin Clindamycin
Penicillin-resistant *Streptococcus pneumoniae*	Vancomycin 1 g every 12 h	L-Ofloxacin
Enterococcus spp.	1 g Ampicillin every 6 h 1 g Vancomycin every 12 h	Ampicillin–sulbactam
Enteric Gram-negative rods	750 mg Quinolone (ciprofloxacin) every 12 h orally	Third-generation cephalosporin
Serratia or *Pseudomonas aeruginosa*	2 g Ceftazidime every 8 h (with aminoglycosides once a day or in multiple doses for at least the first 2 wk)	Imipenem Piperacillin–tazobactam Cefepime (with aminoglycosides)
Anaerobes	600 mg Clindamycin every 6 h intravenously or orally	Amoxicillin–clavulanic acid Metronidazole for Gram-negative anaerobes
Mixed aerobic and anaerobic microorganisms	Amoxicillin–clavulanic acid, 2.0 and 0.2 g, respectively, every 8 h	Imipenem

Data from refs. *32,38.*

intravenous therapy using long term intravenous access catheters (i.e., Hickman catheters) decreases length of hospital stays *(50–52).* Oral therapy using the quinolone class of antibiotics for Gram-negative organisms is currently being used in adults with osteomyelitis *(45).* None of the current quinolones provides optimal antistaphylococcal

coverage, an important disadvantage in view of the rising incidence of nosocomially acquired staphylococcal resistance *(53)*. Further, the currently available quinolones provide essentially no coverage for anaerobic pathogens.

Key Points

- Treatment of common skin infections should be based primarily on clinical indications.
- Human and animal bites are not uncommon and management should include antimicrobial therapy that will cover the oral flora of the animal, the skin flora of the victim, and likely environmental contaminants.
- Osteomyelitis can result in severe morbidity. Acute osteomyelitis can be effectively treated with antibiotics. Long-term parenteral antibiotics, many times administered on an outpatient basis, have become the standard of care for chronic osteomyelitis.

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IV
Special Considerations

16
Strategies for Optimal Antimicrobial Use

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INTRODUCTION

Optimal antimicrobial use is essential in the face of escalating antibiotic resistance. The problem of antibiotic resistance affects all sectors of the health care system—the patient, the health care team, the payor, and the public health system. Previous antibiotic use has consistently been identified as a risk factor for individual colonization with resistant pneumococcus *(1).* Community-wide consumption of antibiotics is strongly associated with infection or colonization with resistant organisms *(2).* Antibiotic resistance has been shown to be proportional to the volume of antimicrobial consumption, and reductions in resistance require a proportional reduction in consumption *(3).* Although there is evidence to document the futility and possible harm of antibiotic therapy for many respiratory tract infections, antibiotic prescribing continues for these primarily viral conditions *(4).*

The overall goal of reducing antibiotic prescribing should be an effort to minimize antibiotic resistance while appropriately delivering quality health care—other goals would include decreasing antibiotic costs and minimizing harm to exposed patients. In Finland, a nationwide reduction in the outpatient use of macrolide antibiotics resulted in a reduction of resistant Group A *Streptococcus* from 16.5% in 1992 to 8.6% in 1996. Practitioners were regulated to substitute macrolides for other antibiotics, and although macrolide use decreased, overall antibiotic use did not change *(5).* Icelandic researchers have reduced the proportion of resistant pneumococcal infections through an intervention program delivered to patients and the health care team *(6).* Effective strategies must be identified, and all groups must promote and participate in efforts to reduce antibiotic resistance. Otherwise, the current concern of a "post-antimicrobial era," in which antimicrobial agents will no longer be effective, may become a reality. In this chapter we present a discussion of a variety of strategies that have been used to promote judicious antibiotic use.

UNDERSTANDING ANTIBIOTIC OVERUSE—GETTING TO THE ROOT OF THE PROBLEM

To identify strategies to reduce antibiotic overuse and resistance, contributing factors must be understood (*see* Table 1). Treatment of respiratory tract infections is a useful illustration, as controlling outpatient antimicrobial use for these conditions is

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Table 1
Factors Contributing to Overuse of Antibiotics

Contributing Factor	Explanation
Experience *(4)*	Provider: habit of antibiotic prescribing initiated in the preantibiotic resistance era Patient: perceived efficacy of prior antibiotic therapy for viral infections
Lack of education *(8–10)*	Provider: suboptimal approach to diagnosis and treatment of common viral and bacterial infections Patient: belief that all infections require antibiotic therapy
Expectations *(16)*	Provider: belief that patients expect an antibiotics prescription, and that lack of prescription will damage the relationship Patient: expectation that antibiotics are effective for common viral infections
Economics *(17)*	Provider: time required to explain the lack of need for antibiotic therapy, importance of patient satisfaction. Patient: lost productivity during illness, need to return to work, need to return child to day care

crucial to controlling overuse and resistance *(1).* In the United States, 75% of all antibiotics prescribed in the outpatient setting each year are for respiratory tract infections *(7).* Overuse of antibiotics may relate to misinformation on the part of the practitioner and patient. For example, when presented scenarios consistent with an upper respiratory tract infection with discolored nasal discharge, physicians, pharmacists, and patients were likely to prescribe, recommend, and desire antibiotics *(8–10).* Diagnostic uncertainty may contribute to physicians prescribing antibiotics for primarily viral infections, to cover the "chance" of bacterial infection. Clinical guidelines have been developed to improve diagnostic certainty with hopes of therefore improving the management of common infections *(11–15).*

Patients' past use of antibiotics for self-limiting illnesses may also influence prescribing, as resolution of symptoms may serendipitously correlate with the course of antibiotics. Barriers to changing provider behavior include satisfying patient expectations without decreasing patient-care productivity. The patient education required to dispel the myth of antibiotic necessity is time consuming, and physicians are often fearful that the lack of prescription may negatively affect the doctor–patient relationship *(16,17).* Patients often request antibiotics for paramedical reasons, such as upcoming examinations or prophylactically for travel, and time constraints often make it easier for practitioners to prescribe than to explain why not to prescribe.

When considering pathogens causing nosocomial infections, improving inpatient antimicrobial use and infection control practices are necessary. Hospitals and their intensive care units are common sites for the breeding of resistant bacteria, which require more expensive antibiotics, lead to prolonged hospitalization, an increase in cost of care, and an increase in morbidity and mortality *(18).* Several societies have

published guidelines for optimizing antibiotic use and curtailing antibiotic resistance in hospitals *(19).* However, these guidelines are primarily based on expert opinion, and must be tailored to each hospital system to target specific problems of antimicrobial resistance, local circumstances, and resources.

IMPLEMENTING CHANGE IN THE HEALTH CARE SYSTEM

Despite the considerable amount of money spent on clinical research, relatively little attention has been given to ensuring that the findings of research are implemented in routine clinical practice. In order to implement changes in medical care, it is important to focus on interventions promoting change, and to target interventions to the appropriate audience. Traditional teaching methods (i.e., didactic lectures and continuing medical education) and other forms of passive dissemination of information (i.e., recommendations for clinical care, clinical practice guidelines, audiovisual materials, and electronic publications) have not been shown effective in changing physician behavior *(20–22).* The publication of new clinical trials is not a reliable method of influencing prescribing, nor is the widespread dissemination of practice guidelines *(20).* Government-sponsored feedback on prescribing patterns has not shown an impact on prescribing habits of general practitioners *(22).* Provision of drug-cost information in the computerized patient record has not been shown to affect overall mean prescription cost or prescribing patterns *(23).*

On the other hand, systematic reviews have documented that educational outreach visits, computerized and manual reminders, and interactive educational meetings (participation of healthcare providers in workshops that include discussion or practice) are effective in promoting behavioral changes among healthcare professionals *(20).* Educational outreach visits, also known as academic detailing, use a combination of techniques to improve physicians' clinical decision making *(24,25).* Multifaceted interventions, which include a combination of audit and feedback, reminders, local consensus processes, and/or marketing are consistently effective interventions *(20).* Point-of-care delivery of clinical guidelines and evidence-based recommendations has been shown to impact clinical practice *(26).* Peer education (physician to physician) to improve quality of care and reduce cost of antibiotic prescribing was effective in office practices *(27).* A multidisciplinary continuous improvement approach as been shown to increase clinical prevention efforts and improve the delivery of diabetes care *(28,29).* Unfortunately, these more effective methods are not routinely used in medical education *(30).* It should be noted that physician-to-physician interventions are extremely expensive to implement on a broad scale and thus tend to be limited to small-scale interventions.

CHANGING TO PROMOTE OPTIMAL ANTIBIOTIC USE

Physicians and other health care providers claim awareness of the problem of antibiotic resistance, created by the overuse of antibiotics. However, given the fact that inappropriate antibiotic use continues, this simple awareness is not sufficient to affect prescribing behavior. Several strategies have been applied to improve antibiotic prescribing in the outpatient and inpatient settings, which focus on the system, provider, and patient (*see* Table 2). These strategies are often implemented in closed health care systems, and consist of tightly controlled interventions. However, when these interven-

Table 2
Strategies to Promote Optimal Use of Antimicrobial Agents

Administrative interventions *(31).*	Denial of claims for inappropriate use Financial incentives and penalties
Antibiotic control programs *(18,19,32–34)*	Antibiotic order forms Automatic stop dates (limiting and optimizing duration of use) Restriction for specific indications Restriction of specific classes Improved diagnostic techniques
Point-of-care decision support *(32,37)*	Computer-assisted management programs
Provider education *(20,24,25,27,30)*	Academic detailing Peer education Local opinion leaders Interactive educational meetings
Clinical guidelines *(40,41,43,44)*	Locally developed with input from participating physicians Developed by an outside party (governmental agency, medical society, etc.)
Audit and feedback *(22,45)*	Generated and delivered by members of the health care team Generated and delivered by an outside party (i.e., governmental agency, health care organization, etc.)
Multifaceted intervention *(47)*	Quality improvement initiatives involving educational interventions (to provider and patient), audit and feedback, etc.

tions are applied to a less restrictive system to a wider array of prescribers, maintaining efficacy remains a challenge.

ADMINISTRATIVE INTERVENTIONS

Administrative mandates can be implemented to change physician behavior, with consequences including claim denial for inappropriate behavior, financial incentives, and penalties for specific behaviors. The first study to report a successful intervention to decrease total antibiotic use in ambulatory practice was a noncontrolled study from the New Mexico Experimental Medical Care Review Organization from 1972 to 1975 *(31).* In this study, provider education and strict review of practice was implemented to improve the use of injectable antibiotics for common respiratory tract infections. If strict prescription review indicated inappropriate use of antimicrobial agents, the payment was denied by the organization. Their initiative was associated with a modest reduction in total antibiotic use for bronchitis, influenza, and upper respiratory infections in this Medicaid population.

ANTIBIOTIC CONTROL POLICIES

Many infectious disease societies have published clinical guidelines to control the use of antibiotics in hospital systems *(19).* Antibiotic control programs are implemented in an effort to optimize antibiotic use while minimizing antibiotic costs *(32).* The success of these programs depends on cooperation of multidisciplinary teams, including hospital administrators, clinicians, infectious diseases specialists, infection control teams, microbiologists, and hospital pharmacists *(18).* All team members must promote basic hospital infection control practices such as hand washing. Pharmacists and infection control teams are involved in monitoring of drug use, surveillance and reporting of antimicrobial resistance patterns, and detection of patients colonized with potentially resistant and communicable bacteria. Antibiotic control programs include antibiotic order forms developed by a team of infectious disease "experts," which reflect preferred dosing intervals. Programs may limit the duration of antibiotic therapy (automatic stop dates), or institute restrictions on antibiotic use for specific indications. Many antibiotic restriction programs require clinical justification for the specific antibiotic order prior to dispensing by the pharmacy. In a 1996 survey, 81% of university-affiliated teaching institutions used antibiotic restriction policies and 56% used official recommendations to guide antibiotic use. More than three quarters of these institutions contacted the provider for noncompliance with restriction policies, and almost half refused to dispense the drug if the prescriber refused to alter the order to meet restrictions *(33).*

Restriction of use of specific antibiotics and antibiotic classes has been effective in altering patterns of resistance in individual institutions. For example, in a 500-bed university-affiliated community hospital, 30–40% of nosicomial *Klebsiella* infections were cephalosporin resistant in 1995 *(34).* An antibiotic control policy was developed that, in general, excluded the use of cephalosporins, without prior approval of an infectious disease expert. In one year, an 81% reduction in hospital-wide cephalosporin use was documented, paired with a 140% increase in imipenem use. Ceftazidime-resistant *Klebsiella* was reduced by 36% in nosicomial infections, but this was accompanied by an increase in imipenem-resistant *Pseudomonas aeruginosa.* Overall, there was a reduction in multiply resistant pathogens, but the continued impact beyond this 1-yr intervention on antibiotic resistance is unknown.

With the increase in methacillin-resistant *Staphylococcus aureus* (nearly 40% of all *S. aureus* isolates in large hospitals) and our current limited treatment options limited to vancomycin, restriction policies are present in most hospital systems *(35).* In a large community hospital system, pharmacists placed a point-of-care reminder detailing the Centers for Disease Control guidelines for prudent use of vancomycin in all patient charts over a 1-yr period *(36).* During this time, appropriate use of vancomycin increased from 59% to 80%, and the use of vancomycin decreased by 75%.

In a broader health care system, the Finnish Study Group for Antimicrobial Resistance was established to address the national problem of erythromycin resistance among Group A streptococci *(5).* This national initiative restricted the use of erythromycin and other macrolide antibiotics in the treatment of respiratory and skin infections in outpatients, and was supported by a publicity campaign by local experts and opinion leaders to Finnish physicians. This initiative led to a decline in use of

macrolide antibiotics from 2.4 defined daily doses per 1000 inhabitants in 1991 to 1.38 in 1992. In return, a decrease in the frequency of erythromycin resistance was noted from 16.5% in 1992 to 8.6% in 1996. It is important to note, however, that overall antibiotic use did not change as a result of this national initiative, and resistance patterns with other antibiotics were not studied.

Antibiotic control policies are usually institutional interventions, creating barriers to inappropriate practices and limiting prescriber autonomy. Administrative interventions may also come from governmental agencies that enforce specific practices by laws, regulations, or recommendations. These policies often require added personnel and must be maintained indefinitely to continue to achieve desired results. Success of antibiotic control policies depends on the definition of success. Antibiotic order forms are effective in controlling antibiotic use and reducing antibiotic costs. Antibiotic restriction policies are effective in altering specific resistance patterns. When held to a more important definition of success, such impact on overall resistance patterns and overall patient outcomes, antibiotic control policies have not been appropriately evaluated. Finally, the "hassle factor" of administrative interventions may create dissatisfaction among practicing physicians.

COMPUTER-ASSISTED DECISION SUPPORT

Integration of data from the microbiology laboratory, pharmacy, medical record, and financial databases can assist physicians in decision making in a timely fashion. Antimicrobial susceptibility data, pharmacokinetic information about the individual patient, specific patient factors, and financial data of antimicrobial choices can be presented to the physician at the point of care, in an effort to improve antimicrobial prescribing, cost, and patient outcomes *(32)*.

Antibiotic costs have been significantly reduced using a computer-assisted management program for antibiotics in a small intensive care unit *(37)*. The computer program recommends antibiotic regimens and courses of therapy for individual patients, and provides immediate feedback to the provider at the point-of-care. During a 1-yr intervention period, in 545 patients managed in the intensive care unit, there was a documented improvement in quality of patient care and medication costs when compared to retrospective data. Decreases were noted in medications administered to patients with known allergies, excess drug dosages, antibiotic-susceptibility mismatches, mean number of days of excessive drug dosages, and adverse events caused by antibiotics. In addition, cost of antibiotics was reduced threefold, as were total hospital costs and hospital length of stay. The advantages of the computerized decision support tool were demonstrated in this study, and allowed for more efficient data retrieval. Physicians therefore had more time available to spend on other medical decisions. However, in systems where the use of computer systems is less prevalent, this intervention might be costly and less effective.

PROVIDER EDUCATION

Many systematic reviews have shown that passive dissemination of information, or passive education, is generally ineffective in changing physician practice *(20,30)*. A more important measure, of course, would be to evaluate the impact of physician education on patient health outcomes, but these data are scarce. When education is tailored to change specific behaviors, and tailored to specific providers or situations, this type

Table 3
Important Techniques Used in Academic Detailing

1. Interviewing prescribers to determine baseline knowledge and rationale for current prescribing patterns
2. Targeting specific categories of physicians and their opinion leaders
3. Defining clear educational and behavioral objectives
4. Establishing credibility as an educator by representing a respected organization, referencing quality and unbiased sources of information, and presenting all aspects of a controversial clinical issue
5. Engaging prescriber participation in educational outreach visits
6. Using graphical materials to enhance the educational message
7. Reinforcing the essential educational methods through repetition
8. Using positive reinforcement of improvement in practice patterns on follow-up visits

Data from ref *(25)*.

of intervention is more effective. Interactive educational meetings, where providers participate in workshops that include discussion or demonstration of skills, have been consistently effective *(20)*. In addition, educational outreach visits or academic detailing has been effective, particularly when the visit is conducted by a peer or local opinion leader. To ensure success, academic detailing activities must include several techniques (*see* Table 3), including assessment of baseline knowledge of each provider, identification of local opinion leaders, and using positive reinforcement of improvements in clinical practice *(25)*.

In an early study, investigators evaluated the effect of three educational methods on antibiotic prescribing in office practices in Tennessee *(27)*. The three educational methods included a mailed brochure, a 15-min visit by a pharmacist (drug educator), and a 15-min visit by a physician counselor. Topics of educational activities were three antibiotics contraindicated for office practice (chloramphenicol, clindamycin, and tetracycline for children < 8 yr old) as a measure of the quality of care, and the use of oral cephalosporins as a measure of the cost of care. Based on their use of the mentioned antibiotics, 372 physicians were selected for the interventions. The mailed brochure had no measurable effect on prescribing, and the pharmacist visit had only a modest effect. The physician visit corresponded with a subsequent 44% reduction in patients receiving contraindicated drugs, and a 21% reduction patients receiving and prescriptions for oral cephalosporins. Therefore, the intervention was effecting in improving the quality of care and reducing the cost of care, particularly when the message was delivered by a peer. Further studies of academic detailing activities have demonstrated a benefit of physician visits and small group education over simple mailing of educational materials *(24,38,39)*.

The advantages of academic detailing programs and education outreach visits include the ability to tailor the discussion to the learners level of understanding and scope of practice. However, programs are very dependent on the peer educator's abilities, as well as the physician's active participation in the discussion. Because most improvement initiatives involve some sort of educational program, the positive aspects of academic detailing programs should be highlighted when possible. More practically speaking, however, the effectiveness of an educational intervention is greatly limited

by the size of the population in which the change is desired. When implementing a change in a small group of physicians, the cost and time involved in academic detailing may be worth the investment. However, it is impractical to think that an academic detailing program could be implemented in a large provider group, such as a health maintenance organization or a state health care plan. The cost to send a drug educator (either peer physician or pharmacist) to meet with each provider in the system would be exorbitant, and even if effective, would only affect prescribing of the target clinical question, such as antibiotic prescribing for common infections. Considering the number of target clinical questions that could be subject for improvement, this method becomes even more impractical outside the research environment.

CLINICAL GUIDELINES

Variation and uncertainty regarding appropriate treatment of common medical conditions, including infectious diseases, may be reduced by adhering to evidence-based clinical guidelines. Clinical practice guidelines are defined as "consensus statements that are systematically developed to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" *(40).* Practice guidelines are often used in educational interventions, and have gained increasing popularity as a means of influencing physicians' practice patterns. Despite their popularity, clinical practice guidelines have failed to, in most circumstances, dramatically change practice patterns. In addition, the impact of clinical guidelines on specific patient outcomes has not been rigorously evaluated. Systematic reviews or meta-analyses of clinical practice guideline efficacy may be required to draw firm conclusions about their usefulness *(41).*

The impact of clinical practice guidelines has been disappointing, and may be accounted for by the belief by physicians that they are not written for practicing physicians, but rather focus on the current state of scientific knowledge *(42).* Physicians also may disagree or distrust guidelines written by governmental agencies or "experts" from other institutions, and are more apt to adopt clinical guidelines when they or their peers are involved in development. Finally, physicians fear the implications of clinical practice guidelines on nonclinical factors such as liability and financial incentives from payors. The cost of developing and implementing clinical practice guidelines should not be dismissed. Delivery of clinical practice guidelines is probably best accomplished during academic detailing exercises, with peer educators, rather than by passive dissemination (i.e., mass mailings).

The treatment of infectious diseases, like that of other common conditions, has been inundated with the development of clinical practice guidelines *(11–15).* In six urban and rural hospitals, a practice guideline for the management of community acquired pneumonia in low-risk patients was evaluated, with the objective to switch from intravenous to oral therapy within 3 d and discharge patients within 4 d of hospitalization *(43).* Guidelines were developed by the research team, and physicians and nurses were selected from each hospital as "champions" to endorse the use of the guideline. Despite multidisciplinary involvement in dissemination of the practice guideline, through educational sessions, the practice guideline had no effect on length of stay or patient outcomes.

In a Midwestern staff-model health maintenance organization, clinical guidelines for treatment of uncomplicated cystitis were developed by local physicians and each clinical practice site determined its own process for guideline implementation *(44).* The

goal of the cystitis clinical practice guideline was to reduce treatment duration, to reduce the use of urine cultures, to increase the number of nurse-coordinated cases, all without compromising patient outcomes. Use of the guideline was associated with desirable changes in antibiotic use, nurse coordination of care, cost of care, with comparable clinical outcomes. Therefore, this guideline designed with local input and tailored implementation was successful in achieving a desirable change in care of patients with uncomplicated cystitis.

With the rising concern of appropriate antibiotic use, there will inevitably be an increased number of clinical practice guidelines for infectious diseases. For practitioners, it will be important to evaluate their impact on process of care, patient care outcomes, and more importantly antibiotic resistance patterns. Advantages of using clinical practice guidelines in educational efforts include the ability to target to those who need the education and streamlining of care the most. However, the cost and labor intensity of implementation is not minor. In addition, the ability of these techniques to succeed outside the research environment is yet to be seen.

AUDIT AND FEEDBACK

Audit and feedback, or any summary of clinical performance, has had variable success on promoting changes in physician behavior *(20).* Audit of physician performance requires a strict review of their practice activities, for a given clinical condition or specific delivery of service. Feedback implies a report on their specific practices or patient outcomes, compared to an external source. The external source may be a published clinical practice guideline, a national average, or the "best practice" among their specific physician group practice *(42).* For an audit and feedback loop to be effective, physicians must first recognize that their practice needs to be improved. Obviously, providers requesting feedback and recognizing a need for change are more likely to be successful in implementing a change. Next, the person receiving the feedback must be able to act on the feedback. In addition, feedback should be provided at the point-of-care, or prospectively, during the providers participation in the care system. Retrospective feedback on what "should have been done" is less effective than feedback that can affect change in future patient care activities.

To demonstrate the effect of unsolicited, retrospective feedback on prescribing, the Australian government conducted a randomized controlled trial *(22).* Feedback on 2 y of prescribing was provided to more than 2000 practitioners, in two sets of graphical displays over 6 mo. Prescribing patterns were compared to peer prescribing, and related to five main drug groups. The intervention group also received educational newsletters related to the drug groups. The control group received no information on their prescribing. There were no demonstrable changes in prescribing in the intervention group when compared to the control group—feedback did not affect the variability in prescribing. Therefore, this unsolicited, government-sponsored feedback data had no impact on individual physician practices.

From the other extreme, a group of physicians performed an internal audit and feedback, examining their use of antibiotics for the treatment of otitis media *(45).* Their examination was based on data presented in the Cochrane review for antibiotic use in otitis media, and they found significant antibiotic prescribing for this common condition *(46).* In their practice, they implemented a new system of care for otitis media

including a patient handout, analgesic treatment, and a deferred prescription for amoxicillin. A similar practice acted as the control group, in which standard treatment regimens were continued. During the 12-mo intervention period, antibiotic prescriptions fell 32% in the intervention practice, but only 12% in the control practice. This successful intervention reflects the physicians' readiness for change, and the internal development of a new system of care.

When efforts to change are borne from within those requiring the change, rather than imposed upon by an outside organization, the likelihood of success is greatly increased. Physicians may perceive an outside audit with feedback as a threat to their clinical competence, self-esteem, or autonomy *(42).* Allowing physicians to determine the external standard for comparison of clinical audits, and providing prospective feedback at the point-of-care, are important factors for success of audit and feedback interventions.

MULTIFACETED INTERVENTIONS

Multifaceted interventions are described as those that combine audit and feedback, point-of-care reminders, local input in clinical guideline development, and the support of local opinion leaders *(20).* Multifaceted interventions may also be referred to as continuous quality improvement (CQI) initiatives, and are often attractive to physicians for several reasons. First, the focus lies on improving the delivery and quality of health care, rather than on individual physician behaviors or the bottom line of cost *(42).* Second, there is no mandate of change in individual physician practice, but rather a focus on the efficiency of delivery of care. Many health care systems are implementing CQI activities in specific areas of patient care and clinical service, but few randomized clinical trials exist to document the benefit of this approach.

The only study to examine a multifaceted approach in the outpatient setting focused on improving the treatment of uncomplicated acute bronchitis in adults *(47).* Four office practices were selected for the study: one practice was provided with a full intervention, one practice received a limited intervention, and two practices served as the control sites. In the full intervention site, household educational materials were mailed to all patients (magnets, pamphlets, a letter from the medical director of the practice) regarding appropriate management of common infections. Office-based educational material specific for acute bronchitis was delivered to the office for the examination rooms. Clinicians were detailed on the patient education activities included in the intervention, and were provided with antibiotic prescribing rates for acute bronchitis at their site during the previous winter. They participated in an interactive educational session on evidence-based management of acute bronchitis, and how to say "no" to patient demands for antibiotics. These sessions were led by the medical director, the opinion leader, of each practice, and were attended by all disciplines. In the limited intervention site, office-based educational materials were distributed to the nursing manager at the practice, and were displayed in the patient examination rooms. The control sites provided usual care.

The study was conducted over a 3-mo period, with baseline data from the same months of the prior year. Although antibiotic prescribing rates were similar among the four practices in the baseline period, prescribing fell significantly at the intervention site (from 74% to 48%) but did not change in the control or limited intervention site in the study period. Prescriptions for nonantibiotic medications (i.e., bronchodilators) did not differ among sites, nor did return office visits for bronchitis or pneumonia. There-

fore, in this focused intervention, antibiotic utilization for acute bronchitis improved in one office practice using a multifaceted intervention.

Ideally, using a multifaceted intervention, tailored to each practice group, would be the ideal way to improve the system of care. Realistically, however, the continued success of such programs in everyday clinical practice is less likely, particularly when the focus of interventions expands to include other acute and chronic illnesses. In addition, the generalizability of this controlled intervention to a wider prescribing community requires further study.

THE ROLE OF VACCINATION IN ANTIMICROBIAL RESISTANCE

To limit the selection of resistant organisms, practitioners should use antibiotics in a judicious manner, and prevent infection by immunizing patients at high risk. In essence, a strategy to decrease the use of antibiotics to treat illness is to implement an intervention to decrease the rate of illness. The effectiveness of vaccination to reduce the incidence of infectious disease has been clearly demonstrated with the use of the *Haemophilus influenzae* type b (Hib) vaccine. Prior to its release in 1988, Hib was the most common cause of bacterial meningitis among young children. Since 1993, invasive disease caused by Hib has declined more than 95% in the United States *(48).* With the prevalence of invasive *Streptococcus pneumoniae* infections in adults and children, pneumococcal vaccine is an important method of preventing infection in high-risk populations. It is currently recommended for all persons > 65 yr of age and for those > 2 yr of age with increased risk for invasive pneumococcal disease due to chronic medical conditions. It is not recommended for children < 2 yr of age due to a lack of sufficient antibody response. Future pneumococcal vaccines will couple the polysaccharide to a carrier protein, similar to the Hib vaccine, to increase the immunogenecity *(49).*

Despite the recommendation for vaccination from various organizations, the vaccine is widely underutilized *(50,51).* The national campaign, Healthy People 2000, has the goal to increase immunizations rates to 60% of people at high risk, including those 65 or older *(52).* Several studies have been conducted to impact the frequency of pneumococcal vaccination in at-risk hospitalized patients *(53).* Chart reminders, integration of vaccine reminders and orders into the hospital computer system, and standing vaccination orders with dedicated nurses to administer the vaccine were all strategies implemented. The most effective strategy appears to be a nurse assigned to vaccinate appropriate patients under the authority of a standing order *(53).* In the outpatient setting, pneumococcal vaccination rates were improved using a letter reminder and physician education; however, only 28% of the at-risk population were vaccinated *(53).* In a Canadian study, reminder letters were associated with a $2–3 cost per additional patient vaccinated *(53).*

Of the 90 pneumococcal serotypes, the vaccine contains the 23 serotypes causing the majority of invasive infections in the United States, and may protect against serologically related serotypes as well *(50,51).* Of the seven serotypes most commonly associated with drug resistance, all but serotype 6A are found in the vaccine. Preliminary data suggests, however, that protection against serotype 6A may be present due to cross-reactivity with type 6B *(54,55).* Other sources state that almost 90% of intermediately susceptible isolates are serotyped in the U.S. vaccine *(56,57).* Despite this information, the pneumococcal vaccine has not been reported to reduce the prevalence of penicillin-resistant *S. pneumoniae.* The pneumococcal vaccine has been shown to prevent pneumococcal pneu-

monia in low-risk groups, but it has not been consistently effective in the prevention of otitis media in children *(57).* It has not been shown to consistently reduce the risk of pneumonia in the highest risk population (> 65 yr, long-term care facility residents), nor affect mortality from pneumococcal pneumonia or other pneumococcal infections in any population *(58).* Until the vaccine is appropriately utilized, the true efficacy in preventing common and serious pneumococcal infections will remain unknown.

CONCLUSIONS

Although specific antibiotic selection and restriction policies in the hospital setting are important in altering microbial susceptibility patterns, an overall reduction in antibiotic use in a wider population, the outpatient setting, is more likely to significantly impact antibiotic resistance. Education of providers, the development and implementation of clinical practice guidelines, audit and feedback activities, and multifaceted interventions have all demonstrated an effect in altering antibiotic prescribing in a research setting. However, the ability to translate these research activities into clinical practice and on a wider basis affect antibiotic use, has not been consistently accomplished. In addition, the use of the pneumococcal vaccine has not been widely adopted, although infection with *S. pneumoniae* continues to threaten various populations. Addressing antibiotic use and resistance is one of the most urgent priorities in confronting emerging infectious disease threats *(59).* All providers must examine their own practices to identify how they can reduce unnecessary antimicrobial use. Professional societies, health care organizations, and the Centers for Disease Control and Prevention must also be involved. With partnerships and cooperation of members of the health care teams, the effectiveness of currently available antibiotics may be sustained and the threat of antibiotic resistance minimized.

Key Points

- Physicians and other health care providers claim awareness of the problem of antibiotic resistance, created by the overuse of antibiotics. However, given the fact that inappropriate antibiotic use continues, this simple awareness is not sufficient to affect prescribing behavior.
- Antibiotic control policies, decision support models, academic detailing, clinical guidelines, audit-and-feedback, and multifaceted interventions have documented efficacy in altering antibiotic prescribing in controlled health care settings.
- The success of interventions in a wider prescribing community is less predictable, particularly when the focus of interventions expands to include other acute and chronic illnesses.
- Another method to limit the selection of resistant organisms is to prevent infection by immunizing patients at high risk. The national campaign, Healthy People 2000, has the goal to increase pneumococcal and other immunizations rates to 60% of people at high risk, including those 65 or older.

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Antimicrobial Resistant Flora in the Hospital

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INTRODUCTION

The role of the hospital microbial flora as pathogens responsible for nosocomial infections has been an area of much debate over the centuries. In early hospitals, established prior to the development of the germ theory, scant attention was paid to any measures aimed at avoiding contamination of wounds, hands, or instruments. These facilities, referred to by Nightingale and others as "pest houses," often failed to meet standards of simple cleanliness. With the general acceptance of the microbial origin of infection in the late 19th century, and the work of Nightingale, Sommelweiss, Lister, and others, the hospitals of the late 19th and early 20th century began to focus attention on the environment as a potential source of the pathogens responsible for infection.

When the discovery of penicillin in the 1940s was followed, in turn, by hospital outbreaks of *Staphylococcus aureus* resistant to penicillin in the 1950s, Hospital Infection Control Committees were formed that focused on the environment and colonized health care workers as the source of these resistant pathogens. Practices originating more in dogma than in science arose that emphasized the routine culturing of items as diverse as infant formulas, floors, linens, and the nares of personnel. Threshold limits for the presence of microbes were arbitrarily established, with action plans to address situations when these limits were exceeded. It was not until the 1960s that the Centers for Disease Control established a division to address hospital nosocomial infections and began rigorously studying the dynamics of hospital-acquired infections. The succeeding decades have witnessed many efforts to identify the true dynamics of the role and modes of transmission of infectious pathogens in the hospital setting. As the introductions of newer classes of antimicrobials were followed, in turn, by the inevitable emergence of microbes resistant to these antimicrobials, factors contributing to the emergence as well as the transmission of resistant microbes were addressed.

Many studies have documented the presence of antimicrobial-resistant pathogens on multiple environmental surfaces. As most pathogens can survive on environmental surfaces, it is not surprising that the random culturing of such surfaces will often yield viral, fungal, and bacterial microbes. However, few of these studies have been able to distinguish between environmental contamination by patients or health care workers and the environment as the source of the pathogens. The consensus after a number of decades of rigorous evaluation is that the environment only occasionally serves as the vehicle and/or reservoir for the transmission of resistant microorganisms.

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It is the contaminated hands of health care workers that are the major mechanism by which patients acquire these pathogens *(1,2).* Maki et al. *(3)* demonstrated this relationship by comparing the hospital flora found on environmental surfaces with organisms colonizing and infecting hospitalized patients. Multiple environmental surfaces were cultured in an old hospital and in a new, previously unoccupied, hospital to which the patients were being moved. Although cultures of the surfaces in the old hospital yielded many pathogens similar to those responsible for the nosocomial infections in the patients, such microbes were absent in the cultures obtained in the new hospital prior to the move. For the 12-mo period after the move to the new facility there was no change in the rate of nosocomial infections nor in the pathogens causing these infections. At the end of 12 mo the environmental surfaces in the new hospital yielded microorganisms that were identical, in species as well as in quantity, to those isolated in the old hospital just prior to the move. Thus it was the patients contaminating the environmental surfaces, rather than the environment serving as a source of bacterial pathogens causing infections in the hospital setting.

RESISTANT PATHOGENS AS A CAUSE OF NOSOCOMIAL INFECTIONS

The observation that infections acquired in the hospital tend to be caused by pathogens that are more resistant to antimicrobials than organisms causing similar infections originating in the community was made decades ago. Two factors seem to account for this difference. First, nosocomial infections tend to be caused by pathogens that are intrinsically more resistant to antimicrobials than pathogens that cause community-acquired infections *(4).* While community-acquired pneumonia is most often caused by *Streptococcus pneumoniae,* mycoplasma, chlamydia, *Haemophilus influenzae,* and, in certain geographic areas, *Legionella,* nosocomial pneumonia is more likely to be caused by the more antibiotic resistant *S. aureus* and *Pseudomonas aeruginosa (4).* Similarly, community-acquired urinary tract infections are primarily caused by *Escherichia coli* and *Staphylococcus saprophyticus,* while nosocomial urinary tract infections will more frequently have enteroccocci or *Pseudomonas aeruginosa* as the pathogens *(4).* In each case, the microorganisms that cause nosocomial infections are intrinsically more likely to be resistant to standard antimicrobials.

Another factor responsible for the greater antimicrobial resistance observed in pathogens producing nosocomial infections is that within a given species hospital-acquired microbes tend to be more resistant to antimicrobials than are community-acquired microbes *(5).* Antimicrobial resistance amongst nosocomial pathogens is a phenomenon that has been observed repeatedly since the first penicillin-inactivating enzymes were observed in nosocomial isolates of *S. aureus* in 1944 *(6).* Many mechanisms for antimicrobial resistance, such as the extended-spectrum β-lactamases in Gram-negative bacilli and Tn21-related genetic elements in Gram-negative bacilli which facilitate the dissemination of resistance genes between organisms, were seen initially, and still remain primarily, in hospital-acquired pathogens *(7).* It is hypothesized that the emergence of these resistance factors in hospital settings is a function of the greater selection pressure created by the great amount of antibiotic use and the clustering of ill and often immunocompromised patients *(8,9).* This concept is supported by the observation that bacteria isolated from infections acquired in the intensive care unit are more likely to be resistant to antimicrobials than similar bacteria

causing infections in non-intensive-care-unit settings *(9–11).* It is in the intensive care unit where we would expect the selection pressure of antibiotic use, together with the clustering of immunocompromised patients, to be at its greatest *(11,12).*

During the past two decades, Gram-positive cocci have become increasingly important as nosocomial pathogens *(10).* Two such bacteria that have been especially problematic, due to their antimicrobial resistance and potential to cause outbreaks, are methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Isolates of *S. aureus* resistant to semisynthetic penicillins were detected shortly after the introduction of these agents in the early 1960s *(13).* Within a very short period of time after their appearance these organisms had spread to Europe, Australia, and finally the United States *(14).*

Outbreaks of MRSA have been reported from both teaching and community hospitals, and long-term care facilities. However, despite an early report of MRSA infections occurring in injecting drug users in the community *(15),* MRSA has remained predominantly an institutionally acquired pathogen *(16).* Within the hospital setting, rates of resistance to semisynthetic penicillins among *S. aureus* isolates range from an average of 14.9% in smaller hospitals to 38.3% in larger hospitals, with some teaching hospitals reporting rates as high as 80% *(17).* As few use methicillin to treat *S. aureus* infections today, the real significance of this pathogen is that MRSA tend to be resistant to a wide range of antimicrobials including the penicillins, cephalosporins, macrolides, and quinolones *(14).* For this reason, some have suggested that the initials MRSA should refer to multiply resistant *S. aureus.* It is this resistance to multiple classes of antibiotics, together with the intrinsic virulence of *S. aureus,* which has made MRSA a formidable pathogen over the last few decades. More recently *S. aureus* with intermediate resistance to vancomycin (VISA) and high-level resistance to vancomycin (VRSA) have been identified *(18).* While the occurrences of these organisms have been rare to date, in at least one hospital these organisms appear to have become endemic *(19).*

VRE were present in low numbers in the United States until the late 1980s. Over the past decade the percentage of enterococci isolated from nosocomial infections that are resistant to vancomycin has risen from 0.3% in 1989 to 7.9% in 1993 *(20)* to more than 10% in 1997 *(21).* While VRE was initially confined to intensive care units, it is now appearing in the non-critical-care units of hospitals *(22).* In 1997 the percentage of enterococci reported as resistant to vancomycin was 23.2% in intensive-care settings and 15.4% in non-intensive-care settings *(23).* As in the case of MRSA, the term vancomycin-resistant enterococcus is a bit misleading, as these organisms may also demonstrate high-level resistant to penicillins and the aminoglycosides *(24).* For this reason, some have begun to use the term VAGRE for vancomycin–ampicillin–gentamicin-resistant enterococci. In contrast with the experience in the hospital environment, surveys of community-acquired infections in the United States have continued to show an absence of VRE *(25,26).* Thus in the United States enterococcal infections acquired in the hospital setting are far more likely to be caused by organisms that are highly resistant to antibiotics than are similar community-acquired infections.

It is of interest that while vancomycin-resistant enterococci in the United States are almost exclusively found in the hospital setting, in Europe such organisms are primarily community in origin. Detailed studies have traced these differences to the use of antimicrobials similar to vancomycin in the animal feeds marketed in Europe. Such

agents are not currently used in the feeds marketed in the United States *(27).* This correlation between antibiotic use and emergence of antibiotic resistance in the non-hospital setting has been used by many to support the concept that the antibiotic resistance seen in hospital-acquired pathogens is secondary to the selection pressure created by frequent use of antimicrobials. Such use would clearly be greater in the intensive care unit than in the regular medical–surgical unit, accounting for the frequent emergence of resistant pathogens in the intensive care unit before spreading to less acute areas of the hospital *(11,12).*

The increase in antimicrobial resistance among Gram-negative bacilli in the hospital setting has been largely due to the acquisition of extended-spectrum β-lactamases (ESBL). Pfaller et al. recently reported that in a survey of bloodstream infections occurring in 50 American medical centers resistance to third-generation cephalosporins and broad-spectrum semisynthetic penicillins was documented in 35–50% of *Enterobacter* spp. and *Citrobacter freundii* isolates *(28).* Most epidemiologic studies have identified poor handwashing practices *(29,30),* multiple procedures *(31),* and the overuse of extended-spectrum β-lactams *(28)* as major risk factors for the transmission of ESBL producing Gram-negative bacilli. While inanimate reservoirs of ESBL-producing Gram-negative bacilli are uncommon, one outbreak of an ESBL-producing strain of *Klebsiella pneumoniae* was traced to contaminated ultrasound coupling gel *(32).*

SPECIFIC INANIMATE AND ANIMATE VECTORS

It is important to recognize inadequate handwashing and the contaminated hand as the major factor responsible for the transmission of resistant pathogens in the hospital setting. One must not, however, unduly downplay the role of other vehicles in such transmission. It is often difficult to demonstrate the importance of environmental contamination in causing nosocomial infections, but there are sufficient examples in the literature of such occurrences to remind us that in certain settings environmental contamination clearly does lead to infection. Shared equipment such as electric thermometers *(33),* stethoscopes *(34),* endoscopes *(35),* breast pumps *(36),* and respiratory equipment *(37)* have all been implicated as vehicles for transmission of resistant pathogens. Similarly, plumbing fixtures have been responsible for outbreaks of resistant *Pseudomonas aeruginosa (38)* and *Enterobacter cloacae (39)* nosocomial infections, and contamination of an antiseptic containing soap led to an outbreak of *Serratia marcescens* infections in a neonatal intensive care unit *(40).*

Animate reservoirs may also play a role in the transmission of resistant bacteria, causing both endemic and epidemic nosocomial infections. The gastrointestinal tracts of both patients *(41–44)* and employees *(41)* have been identified as important reservoirs for resistant pathogens in hospital outbreaks. In the case of *Clostridium difficile,* asymptomatic colonization as well as symptomatic disease of the gastrointestinal tract remains the major reservoir of these organisms in endemic, hyperendemic, and outbreak settings *(45,46).* Colonized as well as symptomatic patients heavily contaminate multiple surfaces in their environment, as well as the hands of a substantial percentage of the health care workers caring for them.

Patients with chronic colonization of the urinary tract may be a source for nosocomial infections with resistant Gram-negative bacilli *(47).* Patients who have infected or

colonized burn wounds with multiply resistant *S. aureus* (MRSA) heavily contaminate their immediate environment *(48,49),* leading to cross-infections in other patients in the unit. Similarly patients having pneumonia with MRSA can heavily contaminate their surroundings *(14).* While health care worker colonization with MRSA is infrequently a source of patient infections, certain health care workers do seem to have a tendency toward shedding the organism into the environment and transmitting the resistant bacteria to patients *(50,51).* Such transmission appears to be more likely when the health care worker has an upper respiratory tract infection or chronic dermatitis.

The epidemiology of resistant microorganisms in the hospital environment involves the complex interplay of antibiotic use; the clustering of ill, immunocompromised patients; and both animate and inanimate vehicles and reservoirs. While the precise origin of these microbes is often not identified, it is clear that excessive antibiotic use creates the environment that promotes their amplification, with such use being greatest in the intensive care unit. As antibiotic use may vary widely between different specialties within the same institution, it should not surprise us that different resistance patterns, and different species of resistant organisms, may be seen in differing areas of the hospital. Under the selection pressure of excessive antibiotic use resistant organisms may reach quite high levels in reservoirs such as the gastrointestinal tract, the urinary tract, and the mucous membranes. Patients so colonized may be totally unrecognized by their care givers, allowing for the heavy contamination of the surrounding inanimate environment. The hands of health care workers caring for these patients may become contaminated by direct patient contact or by contact with the contaminated environment. As hand washing practices in the absence, or often in the presence, of isolation precautions are often not optimal *(2),* the hands of health care workers, contaminated with highly resistant pathogens, readily transmit these organisms to other patients on the unit. It is for these reasons that many feel that any control strategies for containing antimicrobial-resistant pathogens in the hospital setting must include good infection control technique *(11,12,21).*

Key Points

- Bacteria colonizing and infecting patients in the hospital setting are more likely to be resistant to antimicrobials than bacteria in the community setting. Within the hospital, bacteria in critical-care units are more often resistant to antimicrobials than bacteria in non-critical-care areas.
- Antimicrobial usage practices and the clustering of ill, immunocompromised patients in hospitals are the two major factors responsible for antimicrobial resistance in hospital-acquired bacteria.
- Much of the increase in antimicrobial resistance in hospital-acquired bacteria is accounted for by the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and the appearance of extended-spectrum β-lactamases in Gram-negative bacilli.
- Poor handwashing practices account for much of the transmission of antimicrobial-resistant bacteria in the hospital.

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18
Infections in the Immunocompromised Host

Vicki A. Morrison

A variety of medical conditions and other factors can cause defects in the humoral and cell-mediated immune defense mechanisms. Individuals with cancer, neutropenic patients, and recipients of solid organ or bone marrow transplants are at high risk for infection, including infection with resistant organisms.

INFECTIONS IN THE CANCER PATIENT

Clinical Description and Epidemiology

Infections remain a common cause of morbidity, and in some cases mortality, in patients with cancers, both hematologic malignancies and solid tumors. Risk factors for infection in this population are related to humoral and cellular immune defects that are inherent to the primary disease process, as well as the immunosuppression caused by therapy.

Patients with hematologic malignancies may have immunologic defects related to the primary disease process even if they have received no cytotoxic therapy for their disease. A characteristic spectrum of infectious complications may occur in these patients as a result of the specific immune defects. For example, patients with chronic lymphocytic leukemia (CLL) have a variety of immune defects, the most pivotal of which is hypogammaglobulinemia *(1,2).* Low immunoglobulin levels (IgA, IgM, IgG) are more common and profound with advanced stage disease, and are not reversible by therapy, even though a concomitant hematologic response may occur. An association between low immunoglobulin levels and the incidence and/or severity of infections has been demonstrated, although the relationship between the level of a specific immunoglobulin and the risk of subsequent infection is not well established. Several studies have found that low IgA levels predispose to an increased risk of infectious complications *(3).* As infections in CLL patients occur most commonly at mucosal sites such as the upper and lower respiratory tract, at which IgA is present, a clinical rationale for this correlation is present. Defects in cell-mediated immunity and complement may also be present in CLL patients; however, the relationship of these defects to infection risk has not been established.

Defects in humoral immunity are likewise of importance in patients with multiple myeloma *(4).* Hypogammaglobulinemia is also prominent in these patients, resulting from both decreased synthesis and increased catabolism of immunoglobulins. As in

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CLL, the immunogobulin levels decline with disease progression. However, in contrast to CLL, an improvement in hypogammaglobulinemia may accompany a hematologic response to therapy. Humoral responses to immunization are also deficient in these patients. The mechanism of these humoral immune defects is related to impairment in the number and function of the residual polyclonal B cells; additional effects by suppressor T lymphocytes are hypothesized. Cell-mediated immune defects, deficient complement activity, and granulocyte/monocyte functional defects may also be present, although their relationship to infection is less clear. In both CLL and myeloma patients, the resulting deficiency in opsonizing antibodies to common encapsulated organisms also impairs the phagocytic function of the monocyte–macrophage system.

In hairy cell leukemia, T-cell dysfunction as well as quantitative and qualitative defects in granulocytes and monocytes predispose patients to unique infectious complications. Impairment in cell-mediated immunity is also found in patients with untreated Hodgkin's disease; humoral immunity and granulocyte function, however, is intact in these patients. Lastly, two hematologic disorders in which neutropenia is commonly present are myelodysplastic syndrome (MDS) and large granular lymphocytic leukemia (LGLL), the latter being a T-lymphocyte disorder.

In addition to specific immune defects related to the primary disease process, the location of the malignancy, especially a solid tumor or lymphoma, may be crucial in predisposing to infectious complications. Obstruction of the respiratory tract, gastrointestinal (GI) tract, genitourinary (GU) tract, or biliary tract by a tumor mass can result in infection. Central nervous system (CNS) dysfunction resulting from a primary CNS tumor, CNS metastases, or carcinomatous/lymphomatous meningitis may predispose to infections. The loss of a gag reflex can lead to aspiration and pneumonia. Likewise, a neurogenic bladder can result in urinary tract infections.

Therapy administered for the malignancy can result in additional immunosuppression. Cytotoxic chemotherapy may result in disruption of normal barriers to infection, including the skin and mucosa. Chemotherapy also often results in neutropenia, which may be short in duration or prolonged for weeks, resulting in a characteristic spectrum of infectious risk (*see* next section). Some chemotherapeutic agents such as the purine analogs (fludarabine, 2-chlorodeoxyadenosine, deoxycoformycin) result in T-lymphocyte defects; these defects may persist for more than a year after discontinuation of therapy. Corticosteroids are commonly employed in the therapy of lymphoproliferative disorders and can cause qualitative defects in phagocyte function. Radiation therapy can lead to damage of the normally intact, protective mucosal surfaces of the respiratory, GI, and GU tracts, in addition to causing defects in cellular immunity, including phagocyte function. Splenectomy, which is now much less commonly utilized for the staging of Hodgkin's disease patients than several decades ago, may impair antibody production and mononuclear–phagocytic cell function necessary for removing opsonized and nonopsonized bacteria.

Lastly, a variety of iatrogenic complications can cause infections in immunocompromised individuals. The placement of intravenous lines, indwelling catheters in the urinary tract, and stents in obstructed regions such as the biliary tree may predispose to infectious complications. Central venous access devices (CVAD), which have an important role in the care of many cancer and other immunocompromised patients, may result in a variety of infections including local exit site infection, catheter tunnel

infection, or catheter-related bacteremia/fungemia. Integumentary defects from venipuncture, intravenous line placement, or bone marrow biopsy allow introduction of colonizing skin flora, including nosocomial pathogens, past normally intact barriers.

Etiology

In patients with humoral immune defects, bacterial etiologies of infection are the most frequent. In CLL patients, the most common sites of infection are mucosal lined surfaces, especially the upper and lower respiratory tract, but also the urinary tract and skin/soft tissue. Bacteria most frequently isolated from these infections include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and various enteric Gram-negative organisms as *Escherichia coli* and *Klebsiella pneumoniae.* Mycobacterial infections are uncommon in this population. Fungal and viral infections are much less common than bacterial infections, most often occurring in patients with advanced stage disease and/or chemotherapy-induced neutropenia. *Candida* and *Aspergillus* species, and herpesviruses, especially varicella zoster virus (VZV) and herpes simplex virus (HSV), are most frequently isolated in these settings. However, the introduction of purine analogs (such as fludarabine) for the therapy of these patients has altered the spectrum of infections seen. Opportunistic infections with agents such as *Listeria,* mycobacterial species, *Nocardia, Aspergillus* spp., herpesviruses, and *Pneumocystis carinii* have been reported *(5,6).* In results of a large intergroup trial of therapy for CLL, patients treated with fludarabine had more major infections including more herpesvirus infections than patients receiving chlorambucil *(7).*

Although *S. pneumoniae* infections are a classic finding in patients with multiple myeloma, other encapsulated organisms such as *H. influenzae* and *Neisseria meningitidis* may also be implicated in infectious complications. However, in studies from the past three decades, enteric Gram-negative organisms, *Candida,* and *Aspergillus* species have taken on a more prominent etiologic role. These isolates are particularly common in the setting of neutropenia, most often occurring in heavily treated patients and in those with extensive marrow involvement. As in CLL patients, fungal and viral infections are less common than bacterial infections. In addition, there is a predilection for these infections to occur at mucosal surfaces.

In some of the less common leukemic processes, a characteristic spectrum of infections is found. Recurrent bacterial infections, especially involving the skin, sinuses, and perirectal area, complicate the course of patients with large granular lymphocytic leukemia, who generally have concomitant neutropenia. Organisms as *Staphylococcus aureus* and *Pseudomonas aeruginosa* are common isolates, with opportunistic agents being less frequent. In patients with myelodysplastic syndrome, bacterial pneumonia and skin abscesses are common infectious complications *(8).* Likewise in patients with hairy cell leukemia, infections at mucosal sites and the skin/soft tissue with common Gram-positive and Gram-negative bacterial isolates are found. However, disseminated infections with opportunists, especially atypical mycobacteria, but also *Candida, Aspergillus, Pneumocystis,* and cytomegalovirus occur, related to the monocytopenia present in this disease process.

Patients with Hodgkin's disease who have underlying defects in cell-mediated immunity are predisposed to opportunistic infections caused by organisms such as *Listeria, Candida* species, herpesvirus, and *Pneumocystis. S. pneumoniae* bacteremia is

one of the more common serious infections in these patients, most often occurring in the setting of prior extensive combined modality therapy (chemotherapy, radiation therapy) or relapse. Lastly, in the small number of patients who now undergo staging laparotomy with splenectomy, infections caused by encapsulated organisms, including *S. pneumoniae, H. influenzae,* and *N. meningitidis,* may occur, more commonly in children than in adults.

In the patient in whom a tumor mass obstructs a tract or duct, the subsequent infections are most often caused by the typical colonizing organisms at that site. However, nosocomial infections, sometimes with multidrug-resistant organisms, are of great significance in several clinical settings. These include hospitalized patients in whom colonization with hospital-acquired pathogens may occur, patients on broad-spectrum antibiotic therapy with subsequent suppression of normal colonizing flora (especially anaerobes), and patients in whom invasive procedures such as surgery or placement of indwelling catheters have been undertaken. Nosocomially acquired pathogens may have distinctive virulence and antibiotic resistance patterns that may vary from institution to institution. Lastly, infections of indwelling vascular catheters such as CVADs, whether involving the exit site, catheter tunnel, or bloodstream, are most commonly caused by staphylococcal species, with *Staphylococcus epidermidis* being the most common isolate in cases of catheter-related bloodstream infection.

Treatment

In patients with hematologic malignancies such as CLL or multiple myeloma that result in humoral immune dysfunction, a variety of preventive approaches have been studied, although none has been convincingly shown to decrease the risk of fatal infections. There is limited prospective randomized data supporting the use of oral antimicrobial prophylaxis, using agents to cover respiratory tract pathogens in these patients. Prophylaxis with trimethoprim–sulfamethoxazole during initial chemotherapy in a series of myeloma patients has been shown to decrease the incidence of bacterial infection *(9).* Despite limited proof of efficacy, agents such as trimethoprim–sulfamethoxazole or ciprofloxacin are commonly used prophylactically in these patients. A recent retrospective study revealed an increased incidence of VZV infections in CLL patients who received therapy with fludarabine *(7).* However, these initial findings should be confirmed prospectively before antiviral prophylaxis is routinely utilized in these patients.

The response to immunization has been found to be defective in CLL and multiple myeloma patients, which is attributable to defects in antigen presentation and impaired production of antibody. Vaccines studied include those for influenza, diphtheria, typhoid, mumps, as well as pneumococcal vaccines. Despite the lack of proven protective efficacy, these vaccines are commonly utilized in these patients.

Hematopoietic colony stimulating growth factors are advocated for selective use in cancer patients receiving myelosupressive therapy. The routine use of these agents is recommended when therapy with select myelosuppressive regimens is instituted *(10).* The American Society of Clinical Oncology has devised guidelines for the optimal use of these agents for primary and secondary prevention of neutropenia *(11).*

Because of the prominent hypogammaglobulinemia present in many of these patients, the use of immunoglobulin replacement has also been examined. In a large

prospective randomized multicenter trial, the prophylactic administration of intravenous immunoglobulin (IVIG) every 3 wk in patients with CLL resulted in a decrease only in minor or moderate severity bacterial infections, with no impact on the occurrence of major or life-threatening, fungal, or viral infections *(12).* This benefit was not cost effective on subsequent economic analysis *(13).* Lower dose immunoglobulin replacement has also been studied in CLL patients, with variable protective benefit found. Likewise in patients with multiple myeloma, conflicting results have been found with regard to the benefit of prophylactic IVIG in reducing the frequency and severity of infections. The role, if any, of IVIG in the therapy of established infections for patients with either of these disorders has not been well studied. Further studies in this area should focus on identifying high-risk subsets of patients for whom this therapy might be beneficial as well as cost effective.

The approach to antimicrobial therapy of established infections in cancer patients should be based on knowledge of the underlying immune defects and corresponding predisposition for infections due to specific organisms, as well as recognition of the colonizing flora at that site and the potential for colonization with drug-resistant nosocomial isolates in select circumstances. A knowledge of local resistance patterns of nosocomial isolates is important in this regard.

A clinical scenario that warrants special comment in the cancer patient due to its frequent occurrence is that of catheter-related infections. Whereas infection along the catheter tunnel generally requires catheter removal for cure, exit site infections usually resolve with appropriate antimicrobial therapy. The majority of catheter-related bacteremias can be successfully treated without catheter removal. However, in the setting of persistent bacteremia despite the administration of antimicrobials to which the isolate is sensitive, the catheter may need to be removed for eradication of infection. In addition, although not well studied in prospective randomized trials, catheter removal plus appropriate antimicrobial therapy is considered necessary for cure in the setting of catheter-related blood stream infection with isolates such as *Corynebacterium jeikeium, Pseudomonas aeruginosa, Bacillus,* atypical mycobacteria, or *Candida* species.

INFECTIONS IN THE NEUTROPENIC PATIENT

Clinical Description and Epidemiology

Over the past several decades, the use of dose-intensive chemotherapy has become more widespread in the care of patients with cancer, as well as some patients with other disorders such as aplastic anemia. The use of these myeloablative therapies is no longer confined to patients with acute leukemia, but is increasingly utilized for patients with lymphoma or solid tumors such as breast cancer, testicular cancer, and sarcomas. The resulting periods of neutropenia may vary from days to several weeks, although the use of hematopoietic colony-stimulating factors (CSFs) such as granulocyte-CSF and granulocyte/macrophage-CSF can shorten the duration of neutropenia. The infection risk in neutropenic patients is related not only to the absolute neutrophil count (ANC), but also to the rate of decline in the ANC and the duration of neutropenia. As demonstrated more than two decades ago, the risk of infection rises with an ANC of $<1000/mm^3$, but increases exponentially as the ANC declines to below $500/mm^3$.

The definition of fever in this population has been arbitrarily defined as a single oral temperature of ≥38.3°C (101°F) *(14).* At least one half of febrile neutropenic patients are found to have either an established or occult infection; in the subset of patients with an ANC <100/mm^3, ≥20% will be bacteremic. Signs and symptoms of infection may be masked in these patients due to the paucity of neutrophils, making infection diagnosis more difficult. With prolonged neutropenia, integumentary breaks are common in normal and mucosal barriers, predisposing patients to infections with organisms colonizing these sites. A major factor predicting a successful outcome from infection in the neutropenic host is recovery of the granulocyte count.

Etiology

Infections in neutropenic patients most commonly occur at mucosal sites such as the oral cavity, upper and lower respiratory tract, esophagus, colon, and perirectal area, in addition to the skin. The most common etiologic agents of infection are the organisms that normally colonize these sites. The frequent use of broad spectrum antimicrobial agents in these patients has an impact on the colonizing flora, resulting in eradication of the normal flora at mucosal sites, particularly anaerobes, and the potential for colonization and overgrowth by nosocomial and/or drug-resistant isolates, which may be more difficult to treat.

The majority of bacterial infections in neutropenic patients are caused by enteric Gram-negative organisms as *Escherichia coli, Klebsiella pneumoniae,* or *Pseudomonas aeruginosa,* in addition to common Gram-positive isolates such as coagulase-negative staphylococci, *Staphylococcus aureus,* and α-hemolytic streptococci. Fungal infections are most commonly caused by *Candida* species, followed by *Aspergillus.* The use of fluconazole prophylaxis may influence the spectrum of fungi found as colonization and etiologic agents of infection, with the emergence of *Candida krusei* as a common isolate in this setting *(15).* Reactivation of HSV infections is also common.

Treatment

Over the past three decades, much commentary has been published on the approach to and management of the neutropenic patient. In 1990, the Infectious Diseases Society of America (IDSA) published summary guidelines for antimicrobial use in neutropenic patients with unexplained fever *(16).* Subsequently in 1997, the first in a series of practice guidelines commissioned by the IDSA was an update of these earlier practice guidelines *(17).* This benchmark publication remains the best consensus statement of the present recommendations for care in these patients. In summary, institution of parenteral antimicrobials is indicated in all febrile patients with an ANC < 500/mm^3, and also in those patients with an ANC of 500–1000/mm^3 in whom a further decline in the ANC is anticipated. Initial therapy should be one of three regimens: (1) single-agent ceftazidime or imipenem, (2) aminoglycoside plus antipseudomonal β-lactam, or (3) vancomycin plus ceftazidime. The addition of vancomycin should be considered in settings of severe mucositis, quinolone prophylaxis, colonization with methicillin-resistant *S. aureus* or penicillin/cephalosporin-resistant *S. pneumoniae,* obvious catheter-related infection, or hypotension. Routine use of vancomycin for all patients is not advocated, because of concern for the emergence of vancomycin-resistant organisms.

The patient should be reassessed after 3 d of this initial therapy. If an etiology of infection is identified, the antimicrobial coverage should be adjusted to provide optimal coverage for that organism, while still maintaining broad-spectrum coverage. This coverage should then be continued for a minimum of 7 d. If no etiology of the fever has been identified at 3 d, stable patients may be changed to oral therapy with an agent such as a quinolone or cefixime. However, if the patient is persistently febrile at 3 d, consideration should be given to the addition of vancomycin, changing antibiotics, or adding amphotericin B (if still febrile after 5–7 d). The duration of antimicrobial therapy recommended is as follows: stop antibiotics at d 7 if the ANC is ≥500/mm^3 and the patient is afebrile; if the ANC is <500/mm^3 at d 7 and the patient is afebrile, antibiotics may be discontinued if the patient is clinically well, but should be continued if the patient has high risk features such as mucositis or unstable hemodynamic parameters; in the setting of persistent fever, antibiotics should be continued if the ANC is <500/mm^3, but may be discontinued if the ANC is ≥ 500/mm^3 for 4–5 d.

Adjunctive therapy in the febrile neutropenic patient is also addressed in these guidelines. Neither empirical antiviral treatment nor the routine use of granulocyte transfusions is recommended. Likewise, the routine use of hematopoietic colony stimulating factors is not advocated; a similar summary document for the use of these latter agents has been published by the American Society of Clinical Oncology *(11).*

Two large prospective randomized studies have been recently published in which parenteral antimicrobial therapy such as that recommended by the IDSA guidelines was compared to oral therapy with agents as ciprofloxacin plus amoxicillin–clavulanate in febrile neutropenic patients who are considered to be low risk *(18–20).* In both trials, the outcome with oral agents was found to be as effective as parenteral therapy. However, the determination of which patients should be considered as low risk remains potentially problematic, thus deterring widespread use of oral therapy in all neutropenic patients at the present time.

Prophylactic therapy for afebrile neutropenic patients is also addressed in the IDSA guidelines. The potential benefit of this approach must be weighed against the problems of fungal overgrowth, toxicity, and the emergence of antibiotic-resistant bacteria. Ideally if prophylaxis is utilized, it should be continued for as brief a period as possible, and only in select patients. Considerations for the use of oral antimicrobial prophylaxis include anticipated profound neutropenia (ANC < 100/mm^3), mucositis, severe periodontal disease, postobstructive infections, or other immune compromise. Either trimethoprim–sulfamethoxazole or an oral quinolone is suitable for prophylaxis in these settings. The routine use of antifungal prophylaxis with agents such as fluconazole is not currently recommended. Lastly, the importance of good handwashing for those in contact with neutropenic patients cannot be overemphasized.

INFECTIONS IN THE SOLID ORGAN TRANSPLANT RECIPIENT

Clinical Description and Epidemiology

The course of solid organ transplant recipients is often complicated by infectious processes, owing to defects in both cellular and humoral immunity. However in the past several decades, improvements in graft and patient survival and a decline in infection-related mortality have been observed, probably related to better regulation of

chronic immunosuppressive therapy, better selection of transplant candidates, improved antimicrobial prophylaxis, and advances in surgical techniques.

Cell-mediated immune defects predominate in the solid organ transplant recipient. Chronic immunosuppressive administered following transplantation to maintain the recipient organ results in additional immunosuppression. Corticosteroids, although now used in lower dosages than in the past, result in defects in both cell-mediated and humoral immunity, with resultant decreases in both CD4 and CD8 T-lymphocytes and monocytes, and impaired macrophage function. Other immunosuppressive agents employed such as azathioprine, cyclosporine, and tacrolimus also result in significant prolonged defects in cell-mediated immunity. Additional factors that contribute to the type and severity and related mortality of infection in the solid organ transplant recipient include the presence of underlying medical conditions such as diabetes or hepatitis, the specific organ transplanted, and the duration of the surgical transplant procedure. It is recognized that the incidence of infection and subsequent mortality are lowest in renal transplant recipients, and highest in the heart–lung recipients. Liver transplant surgery has its own attendant complications related to the length and technical difficulty of the procedure, and anastomotic connections to nonsterile sites including the biliary tree and intestine.

Etiology

The majority of infections following solid organ transplantation occur within four months of transplant. However, a temporal sequence of infections in the post-transplant period has been recognized *(21).* Most infections that occur within the first month following transplant are either preexistent preoperative infections (such as hepatitis), routine postoperative infections (pneumonia, wound, or line related infections), or reactivated HSV infections. In the following interval of 2–6 mo after transplant, various etiologies of infection are seen. Bacterial infections may involve sites such as the bladder and sinuses; in addition, opportunistic organisms including mycobacteria, *Nocardia,* and *Listeria* may cause infection. Fungal isolates in this period include *Aspergillus* and *Cryptococcus.* Other causative agents include viruses (predominantly cytomegalovirus [CMV], *Toxoplasma,* and *Pneumocystis.*

In the period of > 6 mo following transplant, three clinical groups with characteristic infectious complications are seen. Approximately 60–75% of patients require minimal immunosuppression and have good graft function by this time. In these patients, common infections such as respiratory tract infections, diverticulitis, and cholecystitis may occur. However, these infections may present in an atypical manner or have more serious sequelae due to the chronic immunosuppression. From 10% to 15% of patients will have chronic recrudescent viral infections, which may lead to end-organ damage. Etiologies include papovavirus (BK, JC), which may cause urethral stricture and hemorrhagic cystitis; hepatitis B or C, which may result in subacute or chronic hepatitis; Epstein–Barr virus, a causative agent of post-transplant lymphoproliferative disorders; CMV, which most commonly manifests as retinitis at this time; adenovirus; and VZV. The remaining 10–20% of patients have poor allograft function and are receiving excessive amounts of immunosuppressive therapy due to episodes of acute/chronic allograft rejection. This subset of patients is at greatest risk of life-threatening opportunistic infections; immunomodulatory viruses such as CMV are common causative agents.

The etiologic organisms are often dictated by the site of infection in the solid organ transplant recipient *(22–25).* Skin infections are very common, although rarely life threatening. The most common causative agents are viral, such as herpes simplex virus (HSV) and varicella zoster virus (VZV), with other agents such as *Papillomavirus* and various dermatophytes being less common. The skin may also represent a target organ for disseminated infection, with a variety of bacterial (including atypical mycobacteria), fungal, and viral etiologies. The incidence of wound infections varies with the type of transplant, being most common in liver transplant recipients. Although *S. aureus* is the most common wound isolate, Gram-negative enteric organisms, coagulase-negative staphylococci, and rarely *Mucor* may also be etiologic.

In the era before routine prophylaxis, the incidence of urinary tract infection following renal transplantation ranged from 35% to 80%. However, with the institution of trimethoprim–sulfamethoxazole prophylaxis, this incidence has now dropped to <10%. Common isolates include enteric Gram-negative organisms, *Enterococcus,* and *Candida* species *(26).* Less frequently isolated are *Mycoplasma, Mycobacterium* spp., papovavirus (BK, JC), and CMV.

Frequent sources of septicemia in transplant recipients are the lung, abdomen, biliary tract, urinary tract, skin/soft tissues, and intravascular catheters. Polymicrobial bacteremia is not uncommon, especially in the setting of liver and small intestine transplants. Common isolates are enteric Gram-negative organisms, *Enterococcus, S. aureus, Candida* spp., and CMV *(27).* Nontyphoidal *Salmonella* bacteremia has also been reported in renal transplant recipients.

A variety of pulmonary infections may occur after solid organ transplantation *(28).* Community-acquired pneumonia is frequently seen in these patients, and may be caused by traditional organisms such as *S. pneumoniae,* or other isolates such as respiratory syncitial virus. Although primary pulmonary tuberculous disease may occur in these patients, in one recent large series, 33% of *Mycobacterium tuberculosis* infections were disseminated *(29). Histoplasma, Blastomyces,* and *Coccidioidomyces* may cause pulmonary infections in patients from areas endemic for these fungi. In patients with a prolonged duration of symptoms, diffuse or nodular infiltrates, or nonproductive cough, atypical or opportunistic pathogens need to be considered. Opportunistic organisms such as CMV, *Legionella, Pneumocystis,* and *Aspergillus* may be etiologic agents of pulmonary processes in this population in up to 60% of cases *(30,31).*

Intraabdominal infections may be problematic, especially in patients who have undergone transplant procedures involving the abdomen. *Candida* spp. may cause ulcerative lesions throughout the gastrointestinal tract, as may CMV and HSV. Hepatitis may be viral in etiology (CMV, hepatitis C, VZV, HSV, adenovirus type 5), or be a presentation of disseminated fungal infection with organisms such as *Candida, Aspergillus,* or *Histoplasma.* Liver abscesses and cholangitis may occur in the setting of biliary tract obstruction after liver transplant, and can be caused by various Gram-negative enteric organisms, *Enterococcus,* or anaerobes.

The greatest risk for CNS infections is in the first 4 mo following solid organ transplantation, although these may also occur later in patients whose course is complicated by chronic rejection and intensified immunosuppressive therapy. The presentation of these processes is often subtle, with focal necrologic signs infrequently present. Pyogenic bacteria are uncommonly isolated, while opportunistic organisms such as *Liste-*

ria, Nocardia, Mycobacterium spp., *Aspergillus, Cryptococcus, Toxoplasma,* and *Polyomavirus* are more frequent.

Infections may be transmitted from the donor to the recipient by the allograft. Agents transmitted in this manner include CMV, HSV, hepatitis B and C, human immunodeficiency virus (HIV), and *Toxoplasma gondii.* In addition, outbreaks of infection may occur, either related to the nosocomial flora at the transplant center (which may include drug-resistant isolates), or the water supply (as in *Legionella* outbreaks).

Treatment

The use of various prophylactic antimicrobial agents has resulted in an improved outcome in solid organ transplant recipients owing to the decreased frequency of and mortality from infectious complications. Trimethoprim–sulfamethoxazole prophylaxis has been advocated for a minimum period of 6 mo following transplantation. Not only does this provide prophylaxis against many urinary tract pathogens, it also is protective against organisms such as *Toxoplasma, Pneumocystis, Nocardia,* and *Listeria.* Ciprofloxacin may also be utilized for prophylaxis of urinary tract infections, although its spectrum of coverage is more limited than that of trimethoprim–sulfamethoxazole. Aerosolized pentamidine is an alternative agent for *Pneumocystis* prophylaxis in patients who are intolerant to trimethoprim–sulfamethoxazole *(32).* Although the use of isoniazid prophylaxis is controversial, it may be considered for patients who have additional risk factors for active tuberculous disease or recent skin test conversion, and for recipients of organs from skin test positive donors. Nystatin suspension or clotrimazole troches are used to reduce the risk of candidal infections, especially when patients are receiving broad-spectrum antimicrobials or heightened immunosuppressive therapy, as during episodes of rejection. Prophylactic acyclovir, administered for a month post-transplant in HSV-seropositive recipients, has markedly reduced the incidence of HSV infections. In settings in which immunosuppressive therapy is intensified, such as acute rejection, ganciclovir prophylaxis may be utilized to prevent CMV infection *(33,34).* With any of these prophylactic measures, the potential for development of drug-resistant isolates must be recognized *(35).* Lastly, pretransplant vaccination may be considered to help prevent pneumococcal infection, influenza, hepatitis B, and VZV, although data on the latter are limited.

Treatment of established infection depends on the etiologic agent. The antimicrobial sensitivity pattern of nosocomial isolates should be kept in mind, as these patients may be colonized, and subsequently infected with these isolates. A reduction in immunosuppressive therapy may be indicated in the management of certain viral processes, such as post-transplant lymphoproliferative disorders caused by Epstein–Barr virus.

INFECTIONS IN THE BONE MARROW/STEM CELL TRANSPLANT RECIPIENT

Clinical Description and Epidemiology

In the bone marrow/stem cell transplant recipient, various defects in cell-mediated and humoral immunity contribute to the increased risk for infection. Despite advances in prophylactic and supportive care, infections remain a major cause of morbidity and

mortality in this population. Early in the post-transplant period, prolonged neutropenia occurs secondary to the myelosuppression from the preparative regimen. Integumentary defects, such as those from mucositis and the presence of intravascular catheters represent portals of entry for colonizing organisms. Total body irradiation, when utilized results in additional cellular immune deficiency, including defects in the mononuclear–phagocyte cell system. These defects in T-lymphocyte function, in addition to B-lymphocyte dysfunction, are especially pronounced in the allogeneic transplant recipient. Graft-versus-host disease (GVHD) results in increased immunosuppression, including subnormal immunoglobulin production and a hyposplenic state (with chronic GVHD). Therapy for this complication only adds further to the immunosuppression. Lastly, the use of T-cell-depleted marrow results in pronounced and prolonged deficiencies in CD3, CD4, and CD8 T lymphocytes *(36,37).* The use of peripheral blood stem cell products and the ancillary use of hematopoietic colony-stimulating factors such as GM-CSF have been found to result in a shorter time to engraftment, and thus a briefer period of neutropenia and a lesser risk for infectious complications *(38).*

Etiology

Bone marrow transplantation is associated with a characteristic spectrum of post-transplant infectious complications that occur in relation to the time interval following transplantation *(39).* Although this was initially described in allogeneic transplant recipients, a similar pattern of infection, although with a decreased frequency, is found in autologous transplant recipients. The first three to four weeks after transplantation are characterized by marrow aplasia with marked neutropenia. Bacterial infections caused by common Gram-positive isolates such as *S. aureus,* coagulase-negative staphylococci, and α-hemolytic streptococci, and less commonly Gram-negative enteric organisms predominate in this period *(40).* With the administration of broad-spectrum antimicrobial agents, the normal colonizing flora, including anaerobes is ablated, and replaced by potentially more resistant bacterial isolates and fungi, especially *Candida* species, with subsequent infections caused by these organisms *(41).* In patients who are seropositive for HSV, a high rate of reactivation HSV infections may occur during this period. In addition, HSV may cause pneumonia, hepatitis, and esophagitis. Respiratory syncitial virus infections may also occur in a seasonal pattern. The duration of neutropenia has been shortened by the use of hematopoietic CSFs such as G-CSF and GM-CSF in the immediate post-transplant period. Furthermore, stem cell transplant recipients may have a lower risk of infection *(42).*

The spectrum of infection is different in the period 1 to 3 mo post-transplant. Marrow engraftment with resolution of neutropenia has generally occurred by this time. However, acute GVHD has its onset in allogeneic recipients. Major pathogens observed during this time include CMV, *Aspergillus* species, other non-*Candida* fungi, and *Pneumocystis carinii (43–45).*

After 100 d following transplantation, chronic GVHD may complicate the course of allogeneic transplant recipients *(46).* The incidence of pneumococcal bacteremia rises dramatically, owing to the functional asplenic state induced by the chronic GVHD. Bacterial sinopulmonary infections, especially with encapsulated organisms, also become more common. The incidence of VZV infections, mostly dermatomal but occasionally disseminated, also increases. Infections with CMV continue to occur through

this period. Other infections such as acute hepatitis C infection may also manifest. Catheter-related infections may occur throughout the entire post-transplant period *(47,48)*.

Treatment

Owing to the significant impact of infections on the prognosis for bone marrow transplant recipients, prophylactic antimicrobial use in this population has been extensively studied *(49)*. Both trimethoprim–sulfamethoxazole and quinolone derivatives such as ciprofloxacin have been used for selective gut decontamination, and both are effective in reducing the frequency of bacteremia in the neutropenic period. Trimethoprim–sulfamethoxazole is cheaper, but is associated with a higher incidence of *Clostridium difficile* colitis and Gram-negative infections. However, ciprofloxacin use is complicated by a greater incidence of α-hemolytic streptococcal infections. Because of the occurrence of Gram-positive infections early in the post-transplant period, vancomycin use had been advocated for 1–2 d prior to marrow/stem cell infusion *(50)*. However this practice has been abandoned at many centers, owing to the concern for the development of vancomycin-resistant isolates, especially vancomycin-resistant enterococci and coagulase negative staphylococci.

Antifungal prophylaxis with fluconazole has also been utilized. In a large multicenter prospective randomized trial, the use of fluconazole (vs placebo) was found to result in a significantly decreased incidence of systemic fungal infection *(51)*. Although there were fewer infections caused by *Candida albicans* and *Candida tropicalis,* there was no difference in the occurrence of *Candida krusei* infections, and no major impact on the occurrence of *Aspergillus* infections. However in other trials, the use of fluconazole was associated with higher rates of infection with *Candida krusei* and *Torulopsis glabrata (15)*. Because of the limited ability of prophylactic fluconazole to prevent *Aspergillus* infections, other prophylactic antifungal regimens have been employed, including low-dose amphotericin B, aerosolized amphotericin B, and liposomal amphotericin B *(52,53)*. However, late-onset infections with *Aspergillus* spp. remain a problem despite these prophylactic antifungal approaches.

Antiviral prophylactic measures in this population have been directed against several members of the herpesvirus family. CMV is a major cause of morbidity and mortality in allogeneic, and less so in autologous transplant recipients. Patients who are seropositive for CMV prior to transplantation are at greatest risk, especially if the donor is CMV seronegative. The use of either CMV-negative blood products or filtered blood products has been advocated *(54)*. Prophylactic ganciclovir has been utilized, as has preemptive ganciclovir therapy. In the latter approach, patients identified as being at high risk for CMV disease by CMV antigen detection or polymerase chain reaction (PCR) testing receive ganciclovir prophylaxis *(55–57)*. It is recommended that all CMV-seropositive allogeneic transplant recipients either receive prophylactic ganciclovir for at least 100 d after the transplant, or that CMV screening be performed to identify those patients at risk. In contrast to CMV which most commonly occurs from 1 to 3 mo post-transplant, HSV infections typically have an onset within the first week or two following transplant. The use of acyclovir prophylaxis has markedly reduced the frequency of these infections. Occasional infections with acyclovir-resistant isolates have been reported, but are not common. In contrast to HSV and CMV, the majority of

VZV infections occur at a median of 5 mo post-transplant. Long-term prophylactic acyclovir therapy has not been shown to have a significant impact on the occurrence of these infections, and is not presently recommended.

Either twice weekly trimethoprim–sulfamethoxazole, aerosolized pentamidine, or dapsone may be utilized for *Pneumocystis* prophylaxis in these patients. The treatment is generally given for 6 mo after transplantation in allogeneic recipients, or for a longer period in patients with active GVHD for whom treatment with agents such as corticosteroids is required. Trimethoprim–sulfamethoxazole is also effective in preventing toxoplasmosis following marrow transplantation.

The approach to therapy of established infection is similar to that in other highly immunocompromised hosts. Recovery of neutropenia is an important factor affecting infection outcome in the setting of infections caused by pathogens such as *Candida* and *Aspergillus* species. Immunosuppression, especially that resulting from GVHD and the subsequent treatment administered for this complication also impedes the resolution of these infectious complications.

Key Points

- Patients with CLL and multiple myeloma have hypogammaglobulinemia, but current data does not support the routine use of prophylactic IVIG or IVIG as an adjunct to treatment of infections.
- Catheter related bloodstream infections caused by organisms such as *Pseudomonas, C. jeikeium,* atypical mycobacteria, or fungi require removal of the catheter.
- In febrile neutropenia, empiric antibiotic choice should not include vancomycin, except in specific circumstances (*see* text).
- Trimethoprim–sulfamethoxazole prophylaxis is indicated in most cases for at least 6 mo after solid organ transplantation.
- Prophylactic or preemptive ganciclovir has reduced the incidence of CMV disease after allogeneic bone marrow transplantation.

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19
Future Trends in Antimicrobial Use

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The rapidly expanding challenge of antibiotic resistance impacts on patients across the globe. As the new millennium dawns, drugs for the treatment of many illnesses are becoming limited, more expensive, or in some tragic cases nonexistent. As outlined in the preceding chapters, all medical practitioners must be aware of the implications of drug resistance when prescribing therapy. In its 1992 report, the Institute of Medicine identified antibiotic resistance as one of the emerging disease threats. Tuberculosis and cholera organisms once thought to be nearly eradicated have developed drug-resistant strains and threaten the health of millions of people. Bacteria such as pneumococcus, enterococcus, and *Staphylococcus aureus* have developed resistance at a rapid rate and across multiple antibiotics. It was reported in 1995 that antimicrobial resistance among six common bacteria in U.S. hospitals added more than $600 million per year in direct hospital charges *(1)*.

It is becoming ever clearer that strategies to successfully deal with the rise in antibiotic-resistant pathogens must view this threat as a global problem. The rise in antibiotic resistance is directly related to many human activities. Consequently, what does the future hold for therapy for infectious diseases and antibiotic resistance if behaviors remain unchanged? The purpose of this chapter is to review factors that contribute to the rise in resistant organisms, anticipated trends for resistance in the future, and possible approaches to addressing this critical medical problem.

Many factors contribute to the spread of resistance including:

1. Overuse and misuse of antibiotics
2. Lack of regulation of antibiotic use
3. Failure of infection control procedures in hospitals and other sites such as nursing homes
4. Expanding use of antibiotics in medical settings for diseases not traditionally viewed as infections
5. Expanding use of antibiotics in nonmedical settings.

OVERUSE AND MISUSE OF ANTIBIOTICS

Patient expectations for receiving antibiotics play an important role in the overuse of antibiotics. For example, discolored nasal discharge is a normal self-limited phase of a viral upper respiratory tract infection (URI). Randomized placebo-controlled trials

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have shown no significant effect of antibiotics on purulent rhinitis or discolored nasal discharge *(2)*. The color of sputum is not related to the effectiveness of antibiotics in the treatment of acute bronchitis *(3)*. However, when patients were presented with a scenario of a clinical syndrome that was consistent with, although not labeled as, a "common cold" that was 5 d in duration and accompanied by sore throat, cough, and runny nose with discolored (yellow, green, brown) nasal discharge, 79% thought that antibiotics would be effective *(4)*.

A lack of knowledge of appropriate use of antibiotics is not limited to patients but includes health care personnel as well. The trend toward practicing defensive medicine (i.e., prescribing antibiotics "just in case") has accelerated the development of antibiotic resistance. In a survey of primary care physicians in four geographic areas of the United States, respondents indicated that antibiotics would be prescribed by 59% of the physicians in the URI scenario with discolored nasal discharge *(5)*. In scenarios of acute bronchitis, antibiotics were prescribed in 93% of cases with discolored sputum and 44% of those with clear sputum.

Clinical pharmacists are often seen as "drug experts," routinely being asked to provide patient-specific and clinical information about the use of antibiotics and the management of many infectious diseases. Pharmacists have routinely monitored antibiotic use in the hospital setting with the goals of reducing unnecessary antibiotic use, selecting agents with appropriate spectrum of action, reducing antibiotic resistance, improving outcomes, and reducing overall drug costs. Unfortunately, the recommendations of pharmacists for treatments of URIs and acute bronchitis are similar to those of patients and physicians and are not consistent with available evidence of treatment effectiveness *(6)*.

To decrease overuse and misuse of antibiotics, practitioner prescribing of antibiotics needs to be impacted. In countries such as the United States, in which antibiotics can only be obtained with a valid prescription, the voluntary adoption of appropriate prescribing would be a starting point. Although physician education may be needed, providing physicians and other health care professionals with educational tools, clinical pathways, and feedback about prescribing habits may be a good way to help physicians change practices, and thereby confront the public health problem of antibiotic resistance.

It may be necessary, however, to implement restrictions on antibiotics. Formularies and pharmacy authorization are effective ways of controlling prescribing in some hospitals and other "closed" health care systems. Open systems are more difficult to control without government intervention. It may be necessary to go beyond guidelines and voluntary adherence to guidelines to more restrictive policies.

A second strategy for reducing antibiotic usage is to encourage the development and use of vaccines. Successful development of vaccines is a time-intensive process *(7)*. Further, adherence to vaccine recommendations requires significant work but can be particularly effective. The effectiveness of vaccination to reduce the incidence of infectious disease has been clearly demonstrated with the use of the *Haemophilus influenzae* type b (Hib) vaccine. Prior to its release in 1988, Hib was the most common cause of bacterial meningitis among young children. Since 1993, invasive disease caused by Hib has declined more than 95% in the United States *(8)*. Other vaccines that may have particular utility are a *Streptococcus pneumoniae* conjugate vaccine which is scheduled to

be released soon, as well as an oral typhoid Ty21 a vaccine. If individuals do not have invasive disease the use of antimicrobials will be reduced. Unfortunately, the use of vaccines particularly among adults has not achieved recommended levels.

Finally, an exciting new area of medicine is the potential use of methods other than antibiotics to fight infectious diseases. Modulation of the patient's own immune system may provide alternative or adjunctive approaches to the use of antibiotics for the treatment of infectious diseases. As our understanding of the role of cytokines and other immunomodulators expands, these agents may play a larger role in the treatment of infections. Optimization of nutrition and stress reduction may allow reduction in the incidence of infectious disease and avoid the need for antibiotics *(9).* The use of alternative or complementary methods for treatment and/or prevention of infection is a promising area of future research.

LACK OF REGULATION OF ANTIBIOTIC USE

Initiatives to control resistance must include a global perspective. Local or even country-specific initiatives are important but not sufficient; efforts must be undertaken within the context of a larger global population. Travel and immigration have highlighted the fact that countries are not closed systems and microorganisms do not recognize national borders. All nations, especially developed nations with the resources and expertise, must deal with policies and organisms that originate around the globe. For example, in a surveillance study of typhoid fever in the United States between 1985 and 1994, 72% of the affected patients reported international travel within 30 d before the onset of illness *(10).* Moreover, 30% of the isolates were resistant to either ampicillin, chloramphenicol, or trimethoprim–sulfamethoxazole, and 13% were resistant to all three drugs.

In many countries, antibiotics are either legally available without a prescription, or existing regulations are not uniformly enforced. Studies indicate that in countries with little regulation, a substantial amount of antibiotic misuse occurs *(11).* Data from many countries suggest that self-medication is common and frequently inappropriate *(12–15).* Antibiotics are often purchased without a proper indication, in insufficient quantities, and sometimes even when they are contraindicated. In Bangladesh, for instance, about half of the purchases of antibiotics were in quantities that fulfilled the requirements for a single day's dose *(16).* In a relatively affluent district of Manila, the Phillipines, 90% of antibiotic purchases were for 10 or fewer tablets or capsules *(15).*

The Indian Pharmaceutical Act restricts antibiotics to be dispensed only to someone with a valid, current prescription from an allopathic physician. In a study of pharmacies in India, the pharmacies tended to ignore the law and dispensed drugs for prescriptions from nonallopathic physicians and by self-request *(17).* The median number of tablets or capsules was five. As one client said to justify the self-prescribing behavior, "Whenever I get these symptoms and I go to a doctor, he gives me the same medicine and charges me 10 rupees. So why not just buy the medicine?" The pharmacists saw themselves as business people and rarely offered unsolicited advice to change the purchase.

There may be no simple solutions to improve the use of antibiotics in countries with antibiotics available over the counter. Even instituting regulations on access to medications may not be enough. A key to controlling resistance requires cooperation and

shared belief systems from patients, physicians, and others in the health care system regarding appropriate treatment.

Industrialized countries are not immune to the problem of self-prescription of inappropriate antibiotics. In a town on the U.S. side of the United States–Mexican border, 75% of the respondents had purchased prescription medications in Mexico without a prescription *(18).* Recently, it has been reported that in many of New York City's immigrant neighborhoods, antibiotics are being obtained from pharmacies without a prescription *(19).*

The issue of needing a shared belief system about antibiotics and illnesses is particularly apparent in diverse communities that contain a substantial proportion of immigrants. In a recent study in New York City, nearly one third of the respondents believed that antibiotics should be available over the counter *(20).* Of greater importance, a substantial proportion of individuals obtained antibiotics outside of the avenue of a physician prescription for the condition. Individuals not only use "leftover" medication, but also obtain them directly from pharmacists or outside of the United States. It should be noted that individuals who have used antibiotics for viral respiratory infections in the past are much more likely to obtain antibiotics on their own without a prescription. Thus, these behaviors may be hard to extinguish because even in the United States, where a prescription is necessary to receive antibiotics, the majority of patients with viral respiratory infections receive antibiotics *(21).*

FAILURE OF INFECTION CONTROL PROCEDURES

Hospitals and other health care settings are major breeding grounds for antibiotic resistant organisms. While most practitioners are aware that infection control procedures such as handwashing and compliance with isolation procedures are important, their day to day behavior belies this understanding. Repeated studies have documented that health care practitioners fail to wash their hands when indicated and that physicians are the most likely to be noncompliant *(22).* This clearly facilitates the spread of resistant organisms to additional patients in the health care setting. Renewed emphasis on these basics is necessary for all practitioners.

Lack of knowledge of appropriate isolation procedures and noncompliance with regulations remains a major challenge in health care settings. The importance of following "standard" of "universal" precautions has been repeatedly emphasized but too often ignored. Failure to appropriately isolate patients with multiply resistant organisms has facilitated the spread of these microbes.

The CDC has developed a plan to respond to the threat of emerging infectious diseases including the problem of antibiotic resistance *(23).* A system of surveillance and response has been developed, including the Epidemiology and Laboratory Capacity (ELC) program, the Emerging Infections Programs (EIP) and provider based sentinel networks. A specific charge of the ELC program is to track antimicrobial resistance. EIP priorities include retarding the emergence and transmission of antibiotic resistance. The World Health Organization has a WHONET surveillance systems and a program for antimicrobial resistance monitoring (ARM), and continues its efforts in monitoring drug resistant tuberculosis on a global basis. It is critical that all practitioners interact with these programs, especially by reporting to their local health departments *(24).*

ANTIBIOTICS IN MEDICAL SETTINGS FOR DISEASES NOT TRADITIONALLY VIEWED AS INFECTIONS: THE EXAMPLE OF CARDIOVASCULAR DISEASE

An exciting new area of research is the possible etiologic role of infections in the development of illnesses not traditionally viewed as infectious. The documentation of *H. pylori* as the cause of peptic ulcer disease has led to the use of antibiotics in many patients. The recognition that HHV-8 is the cause of Kaposi's sarcoma suggests that cancers may require treatment with antiviral agents. Currently, infections have been hypothesized to play a role in the development of diseases ranging from neuropsychiatric problems to multiple sclerosis. As more and more of these diseases are found to be due to infection, more and more people will receive courses of antimicrobial therapies, in some cases for prolonged periods of time. The impact of these new therapeutic choices on the development of antibiotic resistance will become clearer over the next few years.

Chlamydia pneumoniae has been associated with atherosclerotic cardiovascular disease in seroepidemiologic studies, by detection of the organism in atherosclerotic plaque, and in animal model studies *(25–28).* The proposed mechanism for atherosclerosis would be a "response to injury" wherein the infection may trigger and aggravate endothelial damage, or alternatively, may create local inflammation of the arterial wall. Indirect effects of the infectious agent such as systemic inflammation with a corresponding increase in C-reactive protein, leukocyte count, and cytokines may also be important.

Retrospective studies have attempted to see if patients who were treated with antibiotics, for whatever indication are at lower risk for developing cardiovascular disease events like acute myocardial infarctions. These studies have yielded mixed results with some finding positive associations *(29)* and others finding no relationship *(30).* Two clinical trials to assess the effect of treatment with antibiotics active against *C. pneumoniae* on cardiovascular disease outcomes have indicated a possible effect of the macrolide antibiotics, azithromycin *(31),* or roxithromycin *(32)* in the secondary prevention of coronary heart disease. Other clinical trials have focused on daily 1-mo courses of antibiotics for secondary prevention *(33).*

The effectiveness of prophylactic antibiotic therapy in the primary prevention of CHD has not been evaluated prospectively. Clinical trials of the newer agents for are indicated. It is important to note that none of the studies focusing on the use of antibiotics as treatment for coronary disease includes developing antibiotic resistance in their analysis or models. It is not unimaginable that future medical care may include long-term prophylactic antibiotics for the prevention of coronary disease. The selective pressure of this strategy of antibiotic use in an aging population would be enormous.

EXPANDING USE OF ANTIBIOTICS IN NONMEDICAL SETTINGS: ANIMAL FEED

A great deal of interest has been generated in the link between the use of antibiotics in food animal feeds and the extent to which the practice contributes to the development of antibiotic resistance. Evidence has continued to accumulate suggesting a relationship between the use of antibiotics in animal feed as a growth promoter and the development of resistant pathogens, particularly vancomycin-resistant enterococci (VRE) *(34).* Antibiotics added to animal feed not only reduce the normal intestinal

flora that compete with the host for nutrients but they also reduce harmful gut bacteria, which may decrease performance and growth by causing subclinical disease. The class of antimicrobial drugs used and the animal species involved may determine the relative importance of each mechanism *(35).* Although the quantity of antibiotics used in feed varies, the concentration is often referred to as "subtherapeutic." The resulting concentration in the gastrointestinal tract of the animal is sufficient to inhibit the susceptible bacteria and change the composition of the bacterial gut flora.

In Europe, colonization with VRE appears to occur frequently in persons outside the health care setting. An important factor associated with VRE in the community in Europe has been avoparcin, a glycopeptide antimicrobial drug used for years in many European nations at subtherapeutic doses as a growth promoter in food-producing animals. The use of avoparcin as a growth promoter has created in food animals a major reservoir of *Enterococcus faecium,* which contains the gene bundle for resistance for vancomycin. *E. faecium* is of particular concern because it is present in the normal intestinal flora of nearly all warm-blooded animals, including humans. Furthermore, glycopeptide-resistant strains of *E. faecium* can be transmitted from animals to humans. Two antimicrobial classes expected to provide the future therapeutic options for treatment of infections with VRE have analogs among the growth promoters, and a huge animal reservoir of resistant *E. faecium* has already been created, posing a new public health problem.

Although there are more food animals than humans, the selective pressure favoring VRE in Europe can be estimated to be much higher in food animals than in humans. More of the glycopeptide antibiotic avoparicin was used for growth in animals in Denmark in 1 yr than the amount of vancomycin that was used in all of Europe and the United States used for treating ill humans in the same time period *(36).*

Denmark is illustrative of the problem. VRE are frequently present in food produced in Denmark as well as in food imported into Denmark from other European countries *(37).* Several studies in Europe provide evidence that humans are frequently fecal carriers of VRE *(38,39).* This suggests that VRE can be ingested from food in Europe. Other data in Europe provide additional compelling evidence. Data from the Netherlands that indicates that VRE was not detected in strict vegetarians, suggesting that the source of VRE is contaminated meat *(39).*

It has been suggested that antimicrobial agents should not be used for growth promotion in animals if they are used in human therapeutics or are known to select for cross-resistance to antimicrobial drugs used in human medicine *(34).* Adherence to the World Health Organization recommendations *(40)* will ensure a systematic approach toward replacing antimicrobial growth promoters with safer nonantimicrobial drug alternatives. The European Community countries entered this process in December 1998 when four growth promoters (tylosin, spiramycin, bacitracin, and virginiamycin) were banned because of their structural relatedness to therapeutic antimicrobial drugs used for humans *(41).*

CONCLUSION

We hope that this book helps practitioners to choose optimal antimicrobial therapy for treatment of infectious diseases in their patients. It is clear that the emergence of antimicrobial resistance poses many challenges to both clinicians and their

patients. We have responsibilities both to our individual patients and to the public. Practitioners must avoid the overuse and misuse of antibiotics and educate patients about the potential dangers of unnecessary antibiotics. A renewed emphasis on infection control, infection prevention and vaccination is needed to further reduce the use of antibiotics. Public policy to support world wide public health efforts to monitor and respond to antibiotic resistance is critical, and a global perspective is necessary. New indications for antibiotic use in humans and the use of these drugs in animals must be embarked upon with a heightened awareness of the risks of antibiotic resistance. Antibiotic resistance will change the practice of medicine—we must all be prepared!

KEY POINTS

- Rising antibiotic resistance is a global problem emanating from human activities. Successful strategies to curb this trend will require cooperation and coordinated strategies.
- Several factors play key roles in the trend of rising antibiotic resistance including a lack of regulation of antibiotic use, failure of infection control procedures in hospitals and other sites such as nursing homes, expanding use of antibiotics in medical settings for diseases not traditionally viewed as infections, and the use of antibiotics in nonmedical settings.
- The emergence of antimicrobial resistance poses challenges to society, patients, and clinicians. In industrialized countries it is incumbent upon practitioners to act as first line implementers of strategies to decrease antimicrobial resistance by avoiding the overuse and misuse of antibiotics and educating patients about the potential dangers of unnecessary antibiotics.

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INFECTIOUS DISEASE™

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Management of Antimicrobials in Infectious Diseases

Impact of Antibiotic Resistance

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Optimal antimicrobial use is essential in this era of escalating antibiotic resistance, and an understanding of the appropriate use of antimicrobials, particularly in light of resistant pathogens, is necessary for clinicians engaged in frontline care. In *Management of Antimicrobials in Infectious Diseases: Impact of Antibiotic Resistance,* Arch Mainous, PhD, Claire Pomeroy, MD, and a panel of experienced physicians and antimicrobial experts offer an eminently practical summary of the most effective evidence-based antimicrobial treatments encountered in both hospital and outpatient settings. Focusing on the clinical impact of appropriate diagnosis and treatment, the book emphasizes those newer aspects of infectious disease management necessitated by the growing problem of antibiotic resistance. It also discusses the major pathogens involved so that practicing clinicians will not only diagnose, but also better treat the infections and complications they cause.

Multidisciplinary and highly practical, *Management of Antimicrobials in Infectious Diseases: Impact of Antibiotic Resistance* offers busy clinicians and nurse practitioners a comprehensive and informed guide to navigating the difficult treatment decisions created by the rising tide of antibiotic resistance today.

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- Evidence-based antimicrobial treatment of infectious diseases
- Emphasis on using antimicrobials in the context of antibiotic resistance
- Multidisciplinary approach providing a wide range of expertise and perspectives
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