Management of Antimicrobials in Infectious Diseases

Impact of Antibiotic Resistance

Second Edition

Edited by

Arch G. Mainous III
Claire Pomeroy

Humana Press

Infectious Disease

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Arch G. Mainous III · Claire Pomeroy
Editors

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Editors
Arch G. Mainous III
Department of Family Medicine
Medical University of South Carolina
295 Calhoun St.
Charleston, SC 29425
USA
mainouag@musc.edu

Claire Pomeroy
Department of Medical Microbiology & Immunology
University of California
Davis School of Medicine
Davis CA 95616
USA
claire.pomeroy@ucdmc.ucdavis.edu

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To my wife, Amy.

To my husband, Bill.

Preface

Since the first edition of *Management of Antimicrobials in Infectious Disease: Impact of Antibiotic Resistance* was published in 2001, a myriad of new or increased disease management issues with implications for antibiotic resistance have appeared on the landscape and many continue to challenge us. Consequently, this book has been updated substantially.

The book is intended as a resource to provide practical guidelines for generalist physicians and mid-level practitioners, as well as infectious disease specialists. We designed this book to serve as a resource for evidence-based advice about antimicrobial treatment of infectious diseases encountered in both the hospital and outpatient settings.

Our goal is to facilitate an understanding of commonly encountered infectious pathogens as well as rational approaches to the management of associated diseases. Optimal antimicrobial use is essential in this era of escalating antibiotic resistance and an understanding of appropriate use of antimicrobials, particularly in light of resistant pathogens, is necessary for clinicians engaged in front-line care.

The book focuses on the importance of appropriate diagnosis and treatment of infectious diseases with an emphasis on special aspects of treatment necessitated by the growing problem of antibiotic resistance.

Our book is arranged with chapters focusing on pathogens, followed by chapters focusing on clinical conditions. This strategy was undertaken to provide the clinician two different, yet complementary ways of understanding and managing a clinical problem. In addition, areas such as strategies to promote appropriate antimicrobial use and future trends in treatment and antimicrobial resistance are included to more fully explicate the message of appropriate use of antimicrobials.

It is our hope that this book will disseminate practical knowledge that will improve the quality of medical care and help in addressing the ongoing threat of antimicrobial resistance.

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

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Contents

Contributors

Janet N. Arno Indiana University School of Medicine, Indianapolis, IN, USA

Cristina Baker Staff Physician, Infectious Diseases, Hennepin County Medical Center, University of Minnesota, Minneapolis, MN, USA

Meredith Deutscher Division of Bacterial Diseases, Respiratory Diseases Branch, Centers for Disease Control and Prevention, National Center for Immunizations and Respiratory Diseases, Atlanta, GA, USA

Dimitri M. Drekonja Minneapolis Veterans Affairs Medical Center; Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Martin E. Evans Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine; Lexington Veterans Affairs Medical Center, Lexington, KY, USA

Cindy Friedman Division of Bacterial Diseases, Respiratory Diseases Branch, Centers for Disease Control and Prevention, National Center for Immunizations and Respiratory Diseases, Atlanta, GA, USA

Ivar L. Frithsen Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA

Barry L. Hainer Department of Family Medicine, Medical University of South Carolina, Charleston, SC, US

William J. Hueston Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA

James R. Johnson Minneapolis Veterans Affairs Medical Center; Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Paul Little Community Clinical Sciences, University of Southampton, UK

Arch G. Mainous III Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA

Camelia E. Marculescu Division of Infectious Diseases, Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA

Craig A. Martin Department of Pharmacy Practice and Science, UK HealthCare, University of Kentucky; UK Chandler Hospital, Pharmacy Services H110, Lexington, KY, USA

Eric Matheson Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA

Vicki A. Morrison Staff Physician, Hematology/Oncology & Infectious Disease, Veterans Affairs Medical Center, University of Minnesota, Minneapolis, MN, USA

Avindra Nath Director Division of Neuroimmunology and Neurological infections, Departments of Neurology and Neuroscience, Baltimore, MD, USA

Hien H. Nguyen Division of Infectious Diseases, Division of Pulmonary Critical Care Medicine, Department of Internal Medicine, Davis Health System, University of California, Sacramento, CA, USA

Chris Parsons Division of Infectious Diseases, Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA

Robert E. Post Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA

Frank Romanelli Clinical Specialist in HIV/AIDS, College of Pharmacy, University of Kentucky, Lexington, KY, USA

Cassandra D. Salgado Division of Infectious Diseases, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

Christian Sandrock University of California Davis Health System, Sacramento, CA, USA

Nicoline Schiess Division of Neuroimmunology and Neuroinfectious Disease, Johns Hopkins Department of Neurology, Baltimore, MD, USA

Javeed Siddiqui Division of Infectious and Immunologic Diseases, School of Medicine, University of California Davis, Sacramento, CA, USA

Bojana Stevich Division of Pharmacy, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Vidya Sundareshan Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine, Lexington, KY, USA

Alice C. Thornton Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine, Lexington, KY, USA

Barbara Van Der Pol Indiana University School of Medicine Marion County Health Department, Indianapolis, IN, USA

Antibiotic Resistance and Implications for the Appropriate Use of Antimicrobial Agents

Meredith Deutscher and Cindy Friedman

1 Introduction

Antimicrobial resistance is a major public health threat associated with increased morbidity and mortality as well as enormous healthcare costs that are attributed to longer hospital stays, which require multiple antimicrobial therapies. After recognizing antimicrobial resistance as a phenomenon and the need for a response, the Institute of Medicine published a report in 1998, *Antimicrobial Resistance: Issues and Options* [1]. The report asserted that antimicrobial resistance was accumulating and accelerating while the tools for combating it were decreasing. It was estimated that antimicrobial resistance generated a minimum of $4 billion to $5 billion in costs to U.S. society and individuals annually. Some of the key areas delineated as priorities by the Institute of Medicine report were the following: establishment of surveillance for antimicrobial resistance, understanding the use of antibiotics in food production, prolonging antibiotic effectiveness through educational programs and guidelines for appropriate antibiotic use, developing new products, and regulatory interventions.

In this chapter, we review the epidemiology of resistant pathogens, resistance mechanisms, and methods to measure and monitor antimicrobial resistance. Factors contributing to the development of antimicrobial resistance and measures to control resistance are also discussed. Since these factors differ for community-acquired pathogens and hospital-acquired pathogens, the two groups are considered separately; the main focus is on community-acquired pathogens.

While antibiotic resistance is the focus of this chapter, antiviral resistance is also an important public health issue. For example, antiviral resistance to influenza and HIV has become a problem on a worldwide scale. While discussion of antiviral resistance is beyond the scope of this chapter, tools such as vaccines and diagnosis of nonbacterial pathogens are important components to controlling antibiotic resistance [2–4].

M. Deutscher (✉)
Division of Bacterial Diseases, Respiratory Diseases Branch, Centers for Disease Control and Prevention, National Center for Immunizations and Respiratory Diseases, Atlanta, GA, USA
e-mail: mdeutscher@cdc.gov

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2 Background and Epidemiology of Resistant Pathogens

The number of pathogens exhibiting antimicrobial resistance is increasing. In recent years, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus,* multidrug-resistant tuberculosis, and amantadine/rimantadine-resistant and oseltamivir-resistant influenza virus have all emerged as public health threats [5, 6]. The frequency and level of antimicrobial resistance and the resulting implications on morbidity and mortality ultimately determine the public health impact of resistant pathogens.

2.1 Level of Antimicrobial Resistance

Almost every pathogen has acquired resistance to a therapeutic agent. To be considered a public health burden, resistant pathogens must cause frequent and/or severe infections, be managed with antimicrobial therapy as the standard of care, and have few alternative drugs available for treatment. Several resistant pathogens have created a significant public health burden (Table 1).

Streptococcus pneumoniae is an example of a pathogen that meets these criteria. In 2006, national estimates of invasive pneumococcal disease in the United States were 41,400 cases and 5,000 deaths. Meningitis accounted for 6.1% of cases, and bacteremia without focus accounted for 23.0% [7]. The case/fatality ratio may be higher than 25% for certain high-risk groups with bacteremia and meningitis despite appropriate treatment [8, 9]. In 1994, drug-resistant *S. pneumoniae* became a nationally notifiable disease in the United States, when sporadic reports of increasing infection and the active surveillance data from the Centers for Disease Control and Prevention (CDC) documented an increase in antibiotic-resistant isolates [10]. In 2006, antibiotic susceptibility testing of isolates from CDC's Active Bacterial Core surveillance (ABCs) continued to show a large percentage of resistant isolates; 25.6% were nonsusceptible to penicillin, 21.6% were nonsusceptible to erythromycin, and 22.7% were nonsusceptible to trimethoprim/sulfamethoxazole [7].

Chloroquine-resistant malaria is a problem of public health importance on a global scale. Forty-one percent of the world's population live in areas where malaria is transmitted [11]. Each year, 350–500 million cases of malaria occur, and approximately one million people die of this infection [12]. *Plasmodium falciparum* resistance to chloroquine has been confirmed in almost all areas with *P. falciparum* malaria; exceptions are the Dominican Republic, Haiti, Central America west of the Panama Canal, Egypt, and some other countries in the Middle East [13]. In some regions, as many as 90% of the parasites may be resistant to chloroquine [14]. Major contributors to the development of parasitic resistance have been the limited number of available antimalarial drugs and inadequate dosing for malaria treatment [15, 16].

Table 1 Examples of antimicrobial-resistant microorganisms of public health importance

Microorganism	Mechanisms of resistance	Percent resistance in United States[a]	CDC estimated annual resistant infections in United States	References
Gram-positive bacteria				
Penicillin-nonsusceptible *Streptococcus pneumoniae*[b]	Target alteration: PBP	25.6%	10,600	[7, 31]
Macrolide-resistant *Streptococcus pneumoniae*[c]	Target alteration: ribosomal methylases Active efflux	21.6%	8,940	[7, 113]
Vancomycin-resistant *Enterococcus* (nosocomial)[d]	Target alteration: cell wall Bacterial regulatory system alteration	33%	No estimate	[114, 115]
Methicillin-resistant *Staphylococcus aureus* (nosocomial)	Target alteration: PBP	56%	No estimate	[31, 115–117]
Vancomycin-intermediate *Staphylococcus aureus*[e]	Unknown	Few reported cases in world	<10	[118]
Gram-negative bacteria				
Fluoroquinolone-resistant *Neisseria gonorrhoeae*[f,g]	Target alteration: DNA gyrase and topoisomerase	15.1%	31,900	[119–124]
Third-generation cephalosporin-resistant *Klebsiella pneumoniae* (nosocomial)	Antibiotic modification: ESBLs	24%	No estimate	[39, 115, 116]
Imipenem-resistant *Pseudomonas aeruginosa*	Decreased permeability	24%	No estimate	[34, 115, 116, 125, 126]
Acid-fast bacteria				
INH- and rifampin-resistant *Mycobacterium tuberculosis*	Target alteration or increased target production	0.9% no prior TB 4.2% with prior TB	116 MDR cases	[17, 127]

Table 1 (continued)

Microorganism	Mechanisms of resistance	Percent resistance in United States[a]	CDC estimated annual resistant infections in United States	References
Viruses				
Zidovudine-resistant human immunodeficiency virus[h]	Target alteration: viral reverse transcriptase	1–2% in new cases	400–800[i]	[51, 128–131]
Amantadine/rimantadine-resistant influenza	Modified structural protein (M2 protein)	99.8%[j] 10.6%[k]	5–20% of population infected with influenza annually	[6]
Oseltamivir-resistant influenza[l]	Enzyme modification: mutation in neuraminidase	0%[j] 11%[k] 0%[m]	5–20% of population infected with influenza annually	[6]
Acyclovir-resistant herpes simplex virus[n]	Inhibition of drug activation: mutation in viral thymidine kinase	0.18% (STD clinic) 5.3% (HIV)	No estimate	[132–134]
Fungi				
Fluconazole-resistant *Candida* spp.	Increased drug efflux Target alteration: cytochrome P450 Increased target production Decreased cellular permeability	10.3%[o] 4.0%[p]	No estimate	[135, 136]
Parasites				
Chloroquine-resistant *Plasmodium falciparum*	Increased drug efflux	Widespread worldwide – US disease reflects region of importation	No estimate	[12–16, 37]

Abbreviations: ESBL, extended-spectrum β-lactamase; INH, isoniazid; PBP, penicillin-binding protein; 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 2000 and 2007; see reference for exact year.
[b]Many are also multidrug resistant. Although not listed here, resistance to trimethoprim-sulfamethoxazole is also important.
[c]Erythromycin.
[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]Ciprofloxacin.
[g]Although only fluoroquinolones are listed, quinolones-resistant *N. gonorrhoeae* is also penicillin- and tetracycline-resistant.
[h]Primary mutations associated with zidovudine and other nucleoside reverse transcriptase inhibitors.
[i]Based on an estimate of 40,000 new infections per year.
[j]Influenza A (H3N2).
[k]Influenza A (H1N1).
[l]Amantadine/rimantadine has no activity against influenza B viruses. Oseltamivir and zanamivir have activity against both influenza A and B viruses. CDC recommends the use of oseltamivir and zanamivir for the treatment or prevention of influenza. Use of amantadine or rimantadine is not currently recommended due to high levels of resistance in influenza A (H3N2) viruses. Guidance on influenza antiviral use can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm. Additional information of antiviral resistance can be found at http://www.cdc.gov/flu/about.qa.antiviralresistance.htm.
[m]Influenza B.
[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]*Candida glabrata*. Among North American isolates collected in the ARTEMIS Global Antifungal Surveillance Program, 2001–2002.
[p]*Candida parapsilosis*. Among US isolates collected in the ARTEMIS Global Antifungal Surveillance Program, 2001–2005.

The public health implications of tuberculosis have become more pronounced as the pathogen has become increasingly resistant to antimicrobial therapy. In 2006, approximately 14,000 tuberculosis cases were diagnosed in the United States [17]. Twelve percent of *Mycobacterium tuberculosis* strains in the United States are resistant to at least one drug [18]. A large global survey conducted from 1999 to 2002 by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease documents that the problem of resistance is worldwide; resistant *M. tuberculosis* has been identified in approximately 70 countries and regions. The median prevalence of resistance to any of the first-line antituberculosis drugs in new cases of tuberculosis that were identified in 76 countries and geographical settings was 10.2% (range 0.0–57.1). The median prevalence of multidrug resistance in new cases was 1.0% (range 0.0–14.2) [18]. In the United States, interventions targeting multidrug-resistant tuberculosis (MDR-TB) have had some effect; MDR-TB declined from 2.8 to 1.1% of total tuberculosis cases from 1993 to 1998 [19]. The proportion of MDR-TB cases stabilized and, in 2005, were 1.2% [20].

Gonorrhea, the second most commonly reported notifiable disease in the United States, is another example of an infection where antimicrobial resistance is of great concern. Approximately 14% of isolates tested in 2006 were resistant to fluoroquinolones, which was up from 2.2% in 2002 [21, 22]. Consequently, CDC recommends that treatment now be limited to a single class of antibiotics, the cephalosporins.

2.2 Implications for Morbidity and Mortality

Antimicrobial resistance results in increased morbidity and mortality. In one study that assessed mortality rate in patients with hospital-acquired *S. aureus* bacteremia, the difference between the mortality rates of methicillin-resistant and methicillin-susceptible *S. aureus* was 22.2% [22]. An investigation evaluating patients with MDR-TB showed that only 85% of those with infection 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 [23, 24]. Among patients with resistant tuberculosis that resulted in treatment failure, 40% died [24]. The risk of death following diagnosis with HIV was found to be threefold higher among individuals diagnosed with multidrug-resistant HIV when compared with the overall group of HIV-infected individuals [25]. Resistant pneumococcal meningitis has been associated with persistently infected cerebrospinal fluid [26–28].

Clinicians often prescribe alternate empiric treatment based on knowledge of potential resistance or change treatment based on lack of clinical response, which could lead to an increase in mortality resulting from treatment with an ineffective or less effective drug; how much the case of suboptimal alternative treatment may contribute to the impact of resistance on mortality is unknown. A cause of

increased morbidity and mortality might be that medical management is complicated by drug resistance. Treatment with an antimicrobial to which an organism is resistant can result in treatment failure; thus, resistant infections may result in more serious disease [29].

3 Cell Physiology and Genetics of Antimicrobial Drug Resistance

3.1 Cellular Physiologic Mechanisms

Three physiologic mechanisms cause most antimicrobial resistance: modification or destruction of the antibiotic by enzymes, alteration of the antibiotic target sites, and changes in antibiotic uptake or efflux by the microorganism. Each organism may use one or more of these strategies (Table 1) [30–33].

An example of a bacterium that depends on antibiotic modification is *S. aureus*, which produces the enzyme β-lactamase. This enzyme cleaves β-lactam rings, resulting in inactivation of β-lactam-based antibiotics [31, 33].

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 *S. pneumoniae* produces a different PBP with low affinity for penicillin, it is able to evade the drug's effects [31, 33].

As a result of reduced permeability of their outer layer, bacteria can have decreased uptake of antibiotic. *Pseudomonas aeruginosa* and *Escherichia coli* have an outer membrane with low permeability to antibiotics [34]. 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 the antibiotic imipenem causes *P. aeruginosa* to develop imipenem resistance [34]. 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) [31, 35]. Increased drug efflux is also a mechanism of chloroquine resistance in *P. falciparum* [15, 36, 37].

3.2 Genetic Basis for Resistance

There are three main types of genetic changes that lead to antimicrobial resistance: chromosomal mutations of common resistance genes, acquisition of resistance genes carried on plasmids and other exchangeable genetic segments, and inducible expression of existing genes [31, 33, 34, 38, 39]. Each type of genetic variation has implications on a population level for surveillance and on an individual patient level for clinical management (Table 2).

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* *Staphylococcus aureus*	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) *Staphylococcus aureus*	Nonsusceptibility prevalence can change suddenly, often with several drug resistances linked together	Anticipate co-resistance
Inducible expression	*Enterobacter* Vancomycin-resistant *Enterococcus*	Surveillance is not useful because resistance develops during therapy	Anticipate mid-treatment failure despite initial susceptibility of isolate

3.3 Chromosomal Mutations

Chromosomal mutations in common resistance genes can be spontaneous or can be complex, accumulated mutations (Table 2). For example, *M. tuberculosis* acquires resistance when chromosomal mutations alter the bacterial antibiotic target site or cause the bacteria to overproduce the target [40]. 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 [40]. 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 [40].

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 [41]. Integrons are receptor elements on the chromosome that provide the site into which the gene cassette is integrated and provide the enzyme for integration [41].

One example of the role of these exchangeable gene segments is the plasmid-encoded extended-spectrum β-lactamases (ESBLs) in gram-negative organisms. 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 [42].

The rapid exchangeability of plasmids or other exchangeable gene segments has several implications: (1) surveillance systems need the ability 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. The clinician treating an individual patient must 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). For example, lower respiratory tract pneumococcal isolates recovered from patients younger than 18 years of age in the United States have been shown to have elevated rates of resistance to penicillin, azithromycin, and trimethoprim-sulfamethoxazole, and penicillin resistance correlated with co-resistance to these other antimicrobial agents [43]. Although *S. pneumoniae* co-resistances are not plasmid-borne, they are complex gene mosaics that appear to be tightly linked like those on plasmids.

3.4 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 [44, 45]. Several enterobacteriaceae possess a cephalosporinase that is not normally expressed, but certain cephalosporins will trigger expression of high concentrations of the enzyme [46]. Effective surveillance for these inducible mechanisms is problematic 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.

4 Measuring Antimicrobial Resistance

4.1 Laboratory Testing

Laboratory testing for antimicrobial resistance is generally done using phenotypic assays, although for an increasing number of cases, genotype-based assays can provide rapid information [47, 48].

Phenotypic assays are based on in vitro inhibition of growth of a microorganism in the presence of an antimicrobial. 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) [47, 48]. The MIC is the minimum concentration of antimicrobial 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]) [49, 50].

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; some viruses such as hepatitis B and C, papillomaviruses, and Norwalk-like virus cannot be cultivated at present. While some assays need to be checked to make certain that genotype and clinical phenotype correlate, 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 [49]. Types of assays include sequencing of the microorganism's genome, restriction fragment length polymorphism assays, and line probe assays [49, 51].

Whereas phenotypic testing by disk diffusion for common bacterial resistance requires basic 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 Clinical and Laboratory Standards Institute (CLSI) 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 treated with the usual dosage of the antimicrobial drug [52]. Nonsusceptible refers to the combined categories of full and intermediate resistance. For MICs to be meaningfully interpreted, CLSI takes into account multiple factors when defining the breakpoints for susceptibility for a given antimicrobial agent. These factors include in vitro activity, safety and tolerability of the drug,

pharmacokinetics, achievable tissue concentrations, approved indications and doses, and available clinical data [47, 52].

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 [37]. 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 [37].

4.2 Surveillance

Surveillance is an essential component in the understanding and control of resistance and is helpful in measuring and tracking resistance on a population level. Surveillance has been defined as "a continuous and systematic process of collection, analysis, interpretation, and dissemination of descriptive information for monitoring health problems" [53]. No matter where surveillance data come from, they can be difficult to use for guidance of treatment choices for individual patients. An individual patient might or might 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 [54].

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 initiate contact with those conducting surveillance. Since there are many different permutations of active and passive surveillance, the clinician or public health practitioner must understand the source of the data and the type of surveillance system before applying surveillance data to a given population [53]. Notifiable disease reporting, laboratory-based surveillance systems, and clinics with internal surveillance systems may all provide information about antimicrobial resistance; however, because the methods of data collection differ, estimates of resistance often differ.

Surveillance systems consist of networks of persons carrying out activities on many levels from local to international. 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 public health departments track the prevalence of certain resistant isolates in that state. On the national level in the United States,

CDC has several active surveillance systems that collect population-based resistance data from laboratories around the country for certain bacteria.

Active Bacterial Core surveillance (ABCs) is an example of an active surveillance system that detects the emergence of antimicrobial resistance. ABCs, a component of CDC's Emerging Infections Programs (EIP) network, is an active laboratory- and population-based surveillance system for several invasive bacterial pathogens. For each case of invasive disease in the surveillance population, a case report with demographic information is completed and bacterial isolates are sent to CDC and other reference laboratories for evaluation. ABCs data have been used to track disease trends, such as emerging fluoroquinolone resistance in pneumococcal disease among nursing home residents and decreasing macrolide resistance in pneumococcal disease after the introduction of the pneumococcal conjugate vaccine [55, 56]. Data have also been used to track the emergence of serogroup Y meningococcal disease. Based on data collected by ABCs, a program to assist state and local health departments with surveillance for MRSA and drug-resistant *S. pneumoniae* has been developed.

Heightened surveillance for a particular outcome can be useful for public health goals and for good patient care. Only a handful of vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA, VRSA) infections have occurred throughout the world. Because of the severity of disease with VISA or VRSA, lack of available treatment options, and the potential for emergence of a fully resistant strain, guidelines for heightened passive surveillance were developed. These guidelines encourage enhanced reporting for VISA and VRSA infections so that they can be identified rapidly, interventions can occur, and risk factors for infection can be determined [30, 57].

There are many barriers to population-based surveillance and use of the resulting data [58]. 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 use standardized methods and reporting systems and be able to communicate. There is also a lack of available data correlating local antimicrobial utilization rates with resistance rates; the data would be useful for understanding the drivers of resistance and monitoring interventions. Well-constructed population-based active surveillance has the potential to provide accurate, representative, and timely information on changing rates and patterns of antimicrobial resistance.

5 Factors Promoting Antimicrobial Resistance and Measures to Control Its Spread

5.1 Community-Acquired Pathogens

Antimicrobial exposure is the main factor promoting selective pressure and increasing the development of antimicrobial resistance in the community. Crowding and

Table 3 Types of resistant pathogens and the implications for control measures

	Community-acquired	Hospital-acquired
Definition	Resistant pathogen acquired in the community	Resistant pathogen acquired in hospital
Example	Drug-resistant *Streptococcus pneumoniae*	Vancomycin-resistant *Enterococcus*
Factors associated with increased likelihood of resistance	Recent (previous 3 months) antibiotic use, community with high resistance rates, day care, schools, military	Parenteral antibiotics, prolonged antibiotics, empirical antibiotic therapy, surgical prophylaxis, poor infection control practices
Audience for education	Community medical practitioners, public	Hospital personnel
Control measures	Appropriate antibiotic use by clinician, public education, improved diagnostic techniques, hand washing, vaccines, greater use of animal vaccines	Formulary controls, good infection control precautions (hand washing), cohorting, laboratory surveillance for resistance

other factors also contribute to the spread of resistant organisms (Table 3) [30, 59–61]. While measures to curb the development of resistance among community-acquired pathogens are different for different pathogens, they all rely on some combination of the following tools: (1) vaccines or other measures to prevent disease, (2) development of new antimicrobials to treat resistant infections, and (3) education promoting judicious use of antimicrobial agents to slow or halt development of antimicrobial resistance.

An example of a community-acquired pathogen in which exposure to antimicrobials promotes resistance is *S. pneumoniae* [62]. *S. pneumoniae* is a frequent cause of outpatient respiratory infections, including otitis media, pneumonia, and sinusitis. The strongest risk for developing an infection with drug-resistant *S. pneumoniae* (DRSP) is prior use of antibiotics, in particular during the three previous months [63, 64]. Other risk factors for DRSP infection relate either directly or indirectly to antibiotic exposure. These risk factors include young age, white race, higher income, suburban residence, and day care attendance [63, 65–68]. 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 [65, 67, 68].

Vaccines can prevent disease caused by resistant pathogens. The current 7-valent pneumococcal conjugate vaccine not only reduces carriage of penicillin-susceptible and penicillin-nonsusceptible strains of *S. pneumoniae*, but also reduces rates of invasive disease due to penicillin-nonsusceptible strains. Routine use of this pneumococcal conjugate vaccine to prevent pediatric disease has proved to be a valuable tool in controlling pneumococcal resistance [69, 70]. After vaccine introduction, the rate of resistant invasive pneumococcal disease decreased substantially; between

1999 and 2004, rates of penicillin-nonsusceptible invasive disease due to vaccine strains decreased by 87% [70].

Emerging resistance continues to drive the need for the development of new antimicrobials. Unfortunately, there have been few new antimicrobials developed in recent years. Reasons for the decline of antimicrobial development are generally related to cost. New drug development is estimated to cost $400–800 million per approved agent [71]. Antimicrobials, which are typically used for a short duration, have a lower rate of financial return when compared with drugs that are used to treat chronic illnesses [72]. As a result, pharmaceutical companies may be more likely to promote research and development for drugs used to treat chronic conditions such as hypertension and diabetes. The lack of available guidance from the U.S. Food and Drug Administration (FDA) regarding the types of studies and evidence the FDA considers to be acceptable to demonstrate the safety and efficacy of new drugs has been described as a deterrent to antimicrobial development by pharmaceutical and biotechnology companies [73–75].

Antimicrobials have been overused for acute upper respiratory illnesses (ARIs). Five specific ARIs (upper respiratory tract infections, bronchitis, otitis media, sinusitis, and pharyngitis) account for the majority of ambulatory antibiotic prescriptions [76]. In 1998, there were approximately 84 million ambulatory office visits for ARI, resulting in 45 million antibiotic prescriptions in the United States [77]. An estimated 55% of these antibiotics were used for infections that were unlikely to be bacterial in origin [77]. Because ARIs constitute such a large amount of unnecessary antibiotic use, and because antibiotic use has been associated with carriage of resistant pneumococci and invasive disease, efforts to decrease antimicrobial resistance have focused on judicious use of antimicrobial agents for outpatient ARIs [64, 78–80].

Antibiotic use in children and adolescents, which increased dramatically during the 1980s, began to decline in the 1990s [76]. Still, the numbers of antibiotics prescribed remained high; for example, an estimated 108 antibiotic courses for otitis media per 100 children under age 5 years were prescribed during 1996–1997 [81]. Efforts to discover why physicians continued to prescribe antibiotics inappropriately despite guidance stating otherwise were conducted in the late 1990s. Focus groups with parents, pediatricians, and family physicians have highlighted differences in physician and parent perceptions about antimicrobial use [82]. Parents state that they want a clear explanation when a provider decides not to prescribe an antibiotic. Parents also state that they believe that antibiotics are indicated if their child has green nasal discharge. A third reason that patients seek antibiotics is for a need to return to work, school, or day care quickly. There is a perception that antibiotics speed recovery from upper respiratory tract infections. Physicians indicate that antibiotic prescribing could be safely reduced, but feel pressured to prescribe antibiotics because of diagnostic uncertainty surrounding ARI diagnosis (i.e., no test to help them determine that the infection is viral) and because the short amount of time they have with each patient does not allow time to explain the rationale for not prescribing an antibiotic.

A variety of educational interventions address the problem of antibiotic overuse. Educational interventions aimed at consumers include fact sheets and brochures for parents of young children. These provide answers to commonly asked questions about using antibiotics for upper respiratory infections. Posters designed for use in doctors' offices, clinics, and other healthcare facilities raise awareness about appropriate antibiotic use for upper respiratory infections in children (Fig. 1). Educational interventions aimed at physicians include the following: imitation "prescription

Fig. 1 Example of poster targeted at consumers to raise awareness about appropriate antibiotic use

pads" to provide physicians with written recommendations regarding symptomatic management of viral respiratory illness (Fig. 2); practice-based small-group meetings to educate physicians about appropriate antibiotic use; detailing sheets on appropriate use of antibiotics similar to ones used by pharmaceutical companies promoting new antibiotics; and practice guideline development [80, 83].

Several studies have evaluated the impact of both physician and patient interventions (Table 4). In general, the interventions that work best were the ones that were multifaceted and targeted both consumers and providers. One study that evaluated the impact of these consumer and physician multifaceted interventions found a substantial decrease in antibiotic prescription rates for adults diagnosed with bronchitis, from 74% to 48% [84]. Another found a decrease of 19% in solid antibiotic prescriptions per clinician and 11% in liquid antibiotic prescriptions per clinician [42].

To address the growing problem of antimicrobial resistance, in September 2003 CDC launched *Get Smart: Know When Antibiotics Work*, a multifaceted national public service and media outreach campaign to educate consumers and providers about appropriate antibiotic use. The objectives of this campaign are threefold: (1) promote appropriate antibiotic prescribing practices among medical providers, (2) decrease demand for antibiotics for viral upper respiratory tract infections by consumers, and (3) increase adherence to prescribed antibiotics [85]. The campaign provided a kit which included public service announcements and media outreach tools to help state and county partners implement the campaign locally. Partnership development with nonprofit and for-profit entities has helped to expand the reach of the Get Smart program.

Subsequent phases of the program were designed to reach key audiences, including Spanish-speaking and American Indian/Alaska Native populations. The Get Smart program has sponsored the development of educational curricula for medical students and residents and continuing education for healthcare providers and allied health professionals. The Get Smart program maintains a website that features campaign information and resources [85].

So has any progress been made in reducing antimicrobial prescribing rates in the community? National prescribing data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey have shown a 20% decline in antibiotic prescribing from 1995/1996 and 2004/2005 for the five ARI (pharyngitis, otitis media, sinusitis, URI, and acute bronchitis) outpatient diagnoses [86]. While overall use of antimicrobials in ambulatory patients has decreased, use of expensive broad-spectrum antimicrobial agents has risen (Fig. 3) [87].

5.2 Hospital-Acquired Pathogens

Antimicrobial resistance within the hospital setting is addressed by preventing the development of resistance in individual patients with previously susceptible infections and controlling the spread of nosocomial pathogens [32]. CDC's

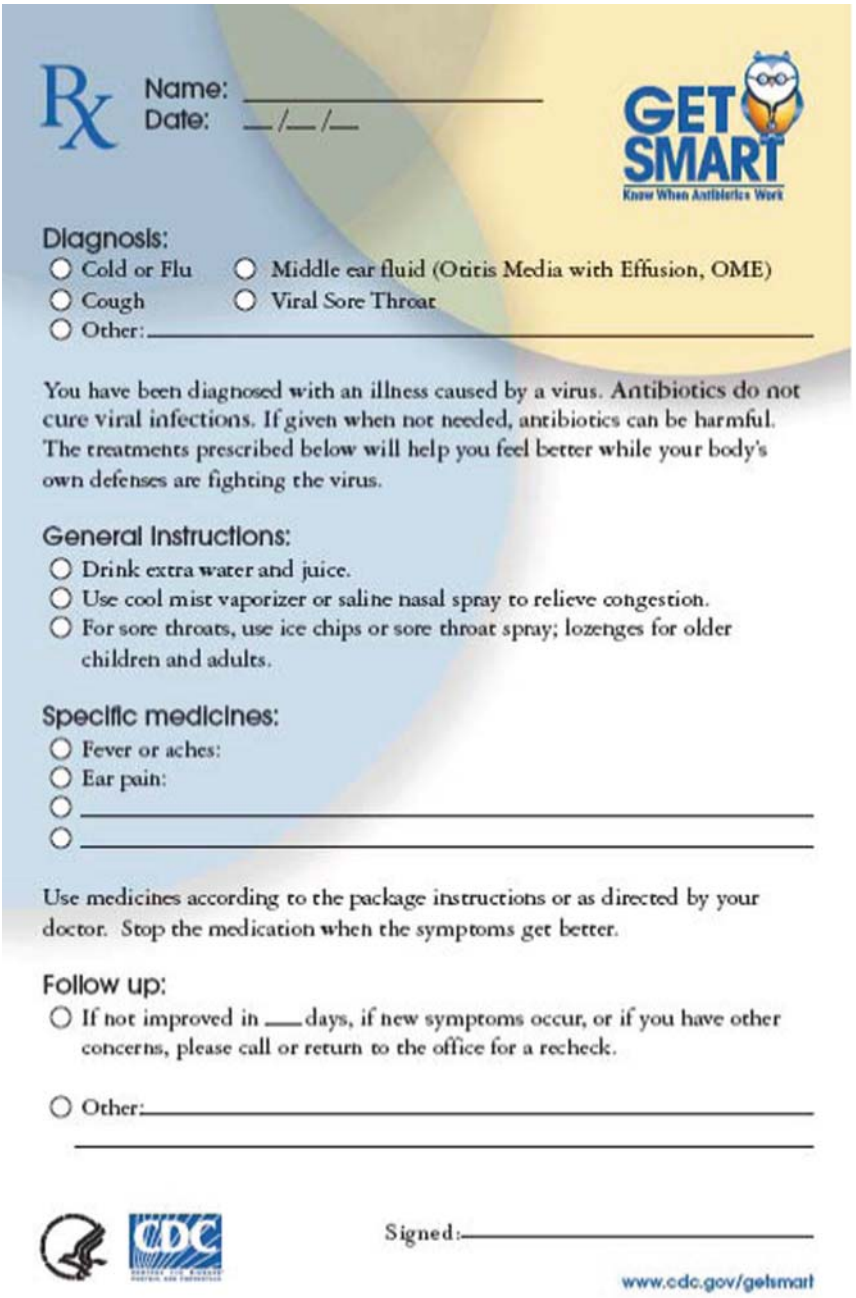


Fig. 2 Example of "prescription pad" with written recommendations regarding symptomatic management

Table 4 Summary of published controlled trials promoting appropriate use of antibiotics [137]

Location of study (year)	Setting	Provider education	Patient education	Public education	Scope	Prescription rate decline	
						Intervention	Control
Denver [84] (1997–1998)	HMO	Prescribing rate feedback, small-group presentations, and practice tips for withholding antibiotics (full intervention sites only)	Office-based educational materials including posters for exam rooms and patient information sheets (limited and full intervention sites) Household mailing to patients including pamphlets, refrigerator magnets, and letter from clinic director (full intervention sites only)	No additional efforts aimed at general public	Adult bronchitis only	35% (for full intervention site)	3%
Boston/Seattle [138] (1997–1998)	HMO	Small-group office presentations led by pediatrician "peer leaders," prescribing rate feedback	Brochures mailed to patients at home; posters and pamphlets in waiting rooms and exam rooms	No additional efforts aimed at general public	Respiratory conditions among children less than 6 years old	18.6% (3–< 36 month old) 15% (36–< 72 month old)	11.5% (3–< 36 month old) 9.8% (36–< 72 month old)

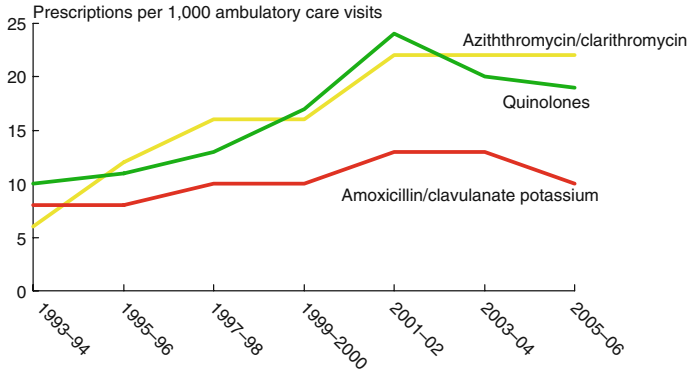
Table 4 (continued)

Location of study (year)	Setting	Provider education	Patient education	Public education	Scope	Prescription rate decline	
						Intervention	Control
Tennessee [139] (1997–1998)	Metropolitan area, medicaid-managed care enrollees	Lectures to targeted providers in multiple settings (primary care clinics, grand rounds, hospital staff meetings); guideline distribution; articles in county health journal	Brochures distributed to parents of newborns, children in day care and K–3rd grade; patient education materials distributed to targeted providers	Brochures distributed to hospitals, clinics, dentists, persons receiving flu vaccine, and pharmacy clients; TV, radio, and newspaper coverage; public service announcements	Respiratory conditions among children less than 15 years old	19%	8%
Wisconsiu [42] (1999)	Rural communities	Grand rounds presentations; practice-based small-group meetings led by physician educators; guideline distribution; CDC fact sheets, patient education materials, viral prescription pad	Information and educational materials presented to clinics by project nurses; "cold kits" provided to clinics for distribution to adults and adolescents	Education for child care providers, public health agencies, parent groups, and community organizations; educational materials (brochures and posters) distributed to clinics, pharmacies, child care facilities, and schools	Respiratory conditions among children	11% (liquids)[a] 19% (solids)[b]	(+12%) (liquids) 8% (solids)

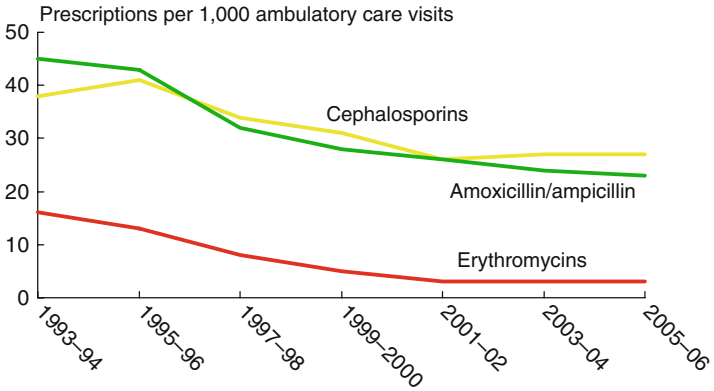
Table 4 (continued)

Location of study (year)	Setting	Provider education	Patient education	Public education	Scope	Prescription rate decline	
						Intervention	Control
Alaska [140] (1998–2000)	Rural villages	Workshops for community health aides and physicians		Presentations at village-wide meetings; health newsletters mailed to homes; high-school education; health fairs	Respiratory conditions among children and adults	31%	9.5%

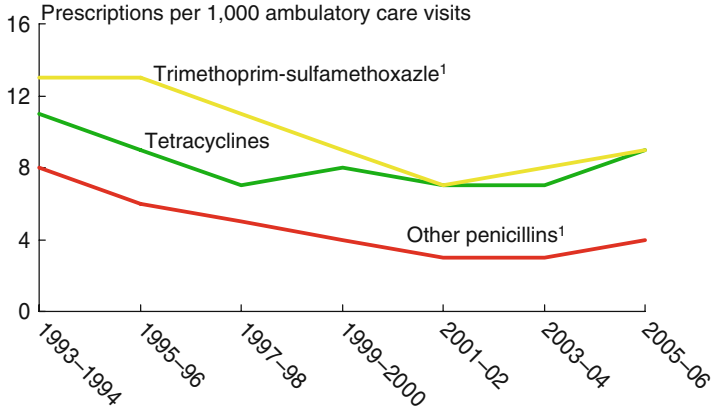
[a] Liquid antibiotics.
[b] Solid antibiotics.



NOTE: All trends shown are significant ($p < .01$). Quinolone estimates are for persons >=15 years of age.
SOURCE: CDC/NCHS, NAMCS/NHAMCS, 1993–2006.



NOTE: All trends shown are significant ($p < .01$).
SOURCE: CDC/NCHS, NAMCS/NHAMCS, 1993–2006.



NOTE: [1] ($p < .01$).
SOURCE: CDC/NCHS, NAMCS/NHAMCS, 1993–2006.

Fig. 3 Antibiotic prescribing in the ambulatory care setting, 1993–2004

campaign to prevent antimicrobial-resistant infections in healthcare settings set forth measures for control of resistance in hospital-acquired pathogens which include (1) preventing infection, (2) diagnosing and treating infections effectively, (3) appropriate antimicrobial prescribing practices, and (4) preventing transmission [88].

Measures to prevent infection among hospitalized patients include the following: hand hygiene practices, proper catheter insertion and care, and use of specific perioperative measures to decrease the risk of surgical site infections.

Effective diagnosis and treatment of infection will also help control antimicrobial resistance within the hospital setting. Availability of rapid, sensitive, and specific diagnostic tests helps assure that the most appropriate and narrowest spectrum antimicrobial agent is used. Clinicians should base empiric treatment of hospitalized patients with probable nosocomial infections on hospital surveillance antibiograms. Infectious diseases experts should be consulted to address management of complicated infections.

Antimicrobial 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. An example of this is vancomycin-resistant *Enterococcus* (VRE); patients who have had exposure to vancomycin are more apt to develop infections with VRE [89]. VRE was first reported in 1986 and is thought to be associated with the use of orally administered vancomycin for treating antibiotic-associated diarrhea in hospitals. Another example is methicillin-resistant *S. aureus* (MRSA), a pathogen in which resistance is associated with the use of semisynthetic penicillins. Nosocomial infections caused by MRSA have been increasing: 2% of staphylococcal infections in U.S. intensive care units were MRSA in 1974, 22% in 1995, and 64% in 2004 [90]. Resistance of gram-negative organisms to extended-spectrum β-lactam antibiotics is also on the rise. In 1997, among *Klebsiella pneumoniae* strains isolated in the United States, resistance rates to ceftazidime and other third-generation cephalosporins were 6.6%, 9.7%, 5.4%, and 3.6% for bloodstream, pneumonia, wound, and urinary tract infections, respectively [91]. In 2003, 20.6% of all *K. pneumoniae* isolates from National Nosocomial Infection Surveillance System intensive care units were resistant to these drugs [92].

Appropriate antimicrobial prescribing practices is another tool needed to control resistance in hospital-acquired pathogens. Reducing antimicrobial use in order to decrease antimicrobial resistance in the hospital setting is difficult, and strategies are still being developed to address this problem. Instituting antimicrobial practice guidelines or protocols is one strategy hospitals use to decrease inappropriate antimicrobial prescribing [93]. Use of practice guidelines has been associated with stable antimicrobial susceptibility patterns for both gram-positive and gram-negative bacteria [94, 95]. Re-evaluating whether prolonged antimicrobial therapy is actually necessary is another strategy used to decrease antimicrobial resistance. Patients in the intensive care unit who receive long courses of antibiotic therapy are

at increased risk of developing infection with a resistant pathogen [96, 97]. Clinical trials assessing duration of antibiotic treatment on treatment effectiveness found that a shorter course of antibiotics is acceptable for patients with ventilator-associated pneumonia who do not have bacteremia [97–99].

Formulary restrictions and preauthorization requirements for specific agents are also used to control inappropriate antimicrobial use [100]. Implementation of these programs has led to short-term increased susceptibilities among some gram-negative pathogens [101, 102]. The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for developing institutional programs to enhance antimicrobial stewardship note that "formulary restriction and preauthorization requirements can lead to immediate and significant reductions in antimicrobial use and cost" [100].

Hospital clinicians should be educated about the appropriate use of antimicrobials. Good communication between pharmacists, infection control professionals, and clinicians may help facilitate this. 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 [103]. Face-to-face educational interventions have been used to modify suboptimal practices of hospital clinicians. Computer interactions are another educational strategy used to decrease inappropriate prescribing of antimicrobials in the hospital setting. Use of computerized order entry to follow antimicrobial prescribing practices within an institution may help determine which antimicrobial prescribing practices need to be addressed [104]. Computer-interaction systems have been successful in guiding and monitoring antimicrobial prescribing and have decreased the prevalence of multidrug-resistant organisms in certain patient care units [95, 105, 106].

Preventing transmission, another tool in controlling antimicrobial resistance in hospitals, depends on good infection control practices. Spread occurs because patients in hospitals are in close proximity to each other, and there are many opportunities for the transmission of resistant organisms. Transmission can occur by respiratory droplets on the hands of healthcare personnel and visitors, as well as on equipment that has been insufficiently cleaned [107, 108]. Guidelines for preventing transmission of infections in the healthcare setting, published by The Healthcare Infection Control Practices Advisory Committee in 2007, specifically address infection control practices to prevent and control healthcare associated infections. The guidelines include recommendations for the following practices: hand hygiene, personal protective equipment, respiratory hygiene and cough etiquette, patient placement, patient care equipment and instruments/devices, care of the environment, textiles, and laundry, safe injection practices, lumbar punctures, and worker safety [109]. Infection control professionals have successfully provided education and feedback to housekeeping staff to improve cleaning of contaminated environmental surfaces [110]. Direct educational interventions to improve hand hygiene have also been successful [111, 112].

Key Points

- Antimicrobial resistance is widespread and growing in scope. Few resistant infections are completely untreatable, but many are associated with increased morbidity and mortality.
- Efforts to decrease inappropriate use of antimicrobial agents and decrease the antimicrobial pressure that drives natural selection for resistance hold promise for prolonging the life span of currently available antimicrobial agents. Surveillance programs to monitor and track resistance patterns are necessary to determine how best to focus these efforts to control resistance.
- Measures to control resistance depend on the type of setting. Key measures for community-acquired pathogens are vaccines, development of new antimicrobials, and education promoting judicious use of antimicrobial agent. For hospital-acquired pathogens, key measures include preventing infection, effective diagnosis and treatment, appropriate antimicrobial prescribing practices, and preventing transmission.

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Part I
Significant Pathogens

Antimicrobial Resistance Among Epidemiologically Important Gram-Positive Bacteria

Cassandra D. Salgado

1 Introduction

The emergence of antimicrobial resistance among clinically relevant bacteria has resulted in profound changes in the approach to treatment of infections caused by these pathogens. This chapter will focus on three epidemiologically important gram-positive bacteria: *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Enterococcus* species. Common infections due to these organisms, common resistance mechanisms, and available treatment options will be reviewed.

2 *Streptococcus pneumoniae*

The pneumococcus, *S. pneumoniae*, is a gram-positive bacterium that replicates in chains when grown in a liquid medium. In the microbiology laboratory, pneumococci have been traditionally identified by four standard reactions: (1) α-hemolysis of blood agar media; (2) catalase negativity; (3) susceptibility to optochin, and (4) solubility in bile salts. Several characteristics of the organism allow it to produce infection in a susceptible host; however, it is the outer polysaccharide capsule that has received the greatest amount of study and description. The capsule protects the organism against phagocytosis and is responsible for the virulence characteristic of the strain. This capsular antigen provokes a type-specific protective immunity (anticapsular antibodies), which has served as the basis for the serotype identification system of the organism. There are currently 90 different serotypes that have been identified; however, serotypes 6, 14, 18, 19, and 23 are the most prevalent, accounting for the majority of disease worldwide [1]. The cell wall is covalently bound to the capsule and is composed primarily of glycopeptides. It is the antigens contained within the cell wall that cause the profound inflammatory reaction among

C.D. Salgado (✉)
Division of Infectious Diseases, Medical University of South Carolina, Charleston, SC, USA
e-mail: salgado@musc.edu

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infected hosts. Other components of the cell wall are responsible for attachment of the organism and then subsequent entry into activated host cells. Activated host cells up-regulate platelet-activating receptors on their surface. Phosphorylcholine, a key component in the pneumococcal cell wall, is responsible for inserting the bacteria into these receptors, later to be taken into the cell by an endocytic vacuole. Additionally, most clinically relevant pneumococcal isolates produce an important virulence factor, pneumolysin, which is an effective cytotoxin responsible for injuring neutrophils, endothelial cells, and alveolar epithelia.

S. pneumoniae is a common colonizing organism of the nasopharynx in humans. When cultured at any given single point in time, the prevalence varies by age group, with pneumococci present in 5–10% of adults and 20–40% of children. Infants become colonized with *S. pneumoniae,* on average, at the age of 6 months, and the initial serotype appears to persist for a mean of 4 months. Adults colonized with individual serotypes have been shown to harbor them for shorter periods of time, usually 2–4 weeks [2]. The worldwide rate of invasive pneumococcal disease, defined as isolation of the organism from a normally sterile body site, has been reported as 15 per 100,000 persons, per year [3], and is more common among the very young (less than 2 years of age) and the elderly (more than 65 years of age). Fortunately, recent data from the United States have suggested that the incidence of pneumococcal disease is decreasing, perhaps as a result of the use of the protein conjugate vaccine in children [4].

Because the organism may be present in the nasopharynx, *S. pneumoniae* has been recognized as a common cause of pneumonia, sinusitis, and otitis media. These infections likely occur via direct spread and invasion. Less frequently, *S. pneumo* has been reported as a cause of meningitis, endocarditis, peritonitis, or bone and joint infections. These infections likely occur via hematogenous spread of the organism from transient or persistent bacteremia.

Over the last 40 years, *S. pneumo* has developed resistance to a variety of antibiotics, including that to β-lactams, macrolides, tetracyclines, trimethoprim-sulfamethoxazole, and fluoroquinolones. Factors which increase a patient's risk for having an antibiotic-resistant strain of *S. pneumo* have been described as previous exposure to antibiotics; exposure to day care or pre-school; stay in a nursing home or other long-term care facility; and having a history of a recent respiratory infection (including viral infections). Of all the classes of antibiotic resistance, the most clinically relevant and most studied among *S. pneumo* isolates is that toward penicillin.

Penicillin inhibits *S. pneumo* by binding to proteins on the cell wall. These penicillin-binding proteins (PBPs) are enzymes needed for synthesis of peptidoglycan. When these PBPs become altered, they have much less affinity for penicillin (and often other β-lactams). Traditionally, resistance to penicillin has been described as concentration-dependent. This definition has been based upon achievable drug concentrations in the cerebral spinal fluid (CSF); however, it has been determined that achievable drug concentrations in the CSF are often much lower than what can be achieved in the plasma, inner-ear fluid, or alveolar fluid. Thus, it is important to realize this when considering whether or not an isolate is resistant and may depend

upon where the infection is located. In the microbiology laboratory, *S. pneumo* is defined as susceptible to penicillin when the MIC ≤0.06 μg/mL; intermediately resistant to penicillin when the MIC is 0.10–1.0 μg/mL; and highly resistant to penicillin when the MIC ≥2.0 μg/mL. In the United States, approximately 60% of *S. pneumo* are susceptible to penicillin, 20% have intermediate resistance, and 20% are highly resistant, but this percentage may vary depending on the region [5]. Children are colonized and infected with more resistant strains compared to adults and in general, invasive isolates tend to be more susceptible than those that cause otitis media. Fortunately, in the United States, use of the 7-valent protein conjugate pneumococcal vaccine has resulted in an 80% reduction in invasive disease and a >95% decrease in invasive *S. pneumo* isolates which are covered by the vaccine [4]. However, not entirely unexpected, there has been an increase among strains that are not covered in the vaccine (type 6 (non-B), 19 (non-F), 35, 11, and 15) and, unfortunately, these strains have demonstrated resistance to antibiotics, as well. Resistance to cephalosporins follows a similar concept and susceptibility to ceftriaxone, a common third-generation cephalosporin used for treatment of *S. pneumo* infections, is defined in the microbiology lab as follows: susceptible if the MIC <1.0 μg/mL; intermediately resistant if the MIC = 2.0 μg/mL; and resistant if the MIC >4.0 μg/mL.

Also important to consider when making treatment decisions is that in the United States, almost 30% of *S. pneumo* isolates are resistant to macrolides, but this varies dramatically depending on the region; up to 10% are resistant to clindamycin; less than 5% are resistant to fluoroquinolones (although this may be higher among long-term care facility residents); 20% are resistant to tetracyclines; and almost one-third are resistant to trimethoprim-sulfamethoxazole [5, 6].

Because the achievable drug concentration differs depending on the body site, therapeutic decisions may differ, depending on the site infected. For Example, to treat all but the most resistant *S. pneumo* isolates, recommended first-line antibiotic therapy for otitis media and sinusitis has been higher dose amoxicillin given at 90 mg/kg per day, divided into twice or thrice daily doses. If treatment failure occurs or the patient has a penicillin allergy, one might consider a macrolide antibiotic, and if one suspects cross-resistance to penicillin as well as the macrolide class of antibiotics, alternatives such as clindamycin or a third-generation cephalosporin should be considered. For pneumonia and bacteremia, there is debate regarding whether or not infection due to penicillin-resistant strains is associated with a worse outcome when compared to infection due to susceptible strains. Some studies have shown that the elderly and those with underlying co-morbid conditions do worse when suffering from pneumonia due to a β-lactam-resistant *S. pneumo* and, thus, many recommend a β-lactam plus a macrolide for patients presenting with community-acquired pneumonia where *S. pneumo* is a consideration [7]. For bacteremia in a normal host, most experts recommend cefuroxime, cefotaxime, or ceftriaxone at standard doses, as the plasma levels achievable typically exceed the desired MIC. Meningitis can be associated with extremely poor outcomes when not treated appropriately and the achievable drug concentration in the CSF is lower than that achievable in plasma or alveoli. Thus, the treatment recommendations for meningitis suspected to be due

to *S. pneumo* in an area where isolates exist with intermediate or high resistance to penicillin and/or ceftriaxone (or the patient has risk factors for an antibiotic-resistant strain) are for higher dose third-generation cephalosporins such as cefotaxime 2 g IV q4h or ceftriaxone 2 g IV q12h, plus vancomycin. Of note, vancomycin does not penetrate the blood–brain barrier well, so, once susceptibilities return, if treatment can be continued with a β-lactam, this is desirable.

Unlike many bacteria that cause significant disease, there are vaccines available for prevention of *S. pneumo* infection. The 7-valent pneumococcal conjugate vaccine (Prevnar®), released in 2000, is recommended for children under the age of 2 years. Pneumococcal vaccines for the prevention of disease among children and adults who are 2 years and older are the Pneumovax® and the Pnu-Immune®. These vaccines are 23-valent polysaccharides currently recommended for use in all adults who are older than 65 years and for persons who are 2 years and older and at high risk for disease (e.g., sickle cell disease, HIV infection, or other immunocompromising condition).

3 *Staphylococcus aureus*

S. aureus, a member of the Micrococcaceae, are named after their ability to grow in grape-like clusters in solid media. In the microbiology laboratory, staphylococci are characterized by a positive catalase test and identified as *S. aureus* by a positive coagulase test (indicating the presence of coagulase enzymes). Several virulence factors have been described which may contribute to *S. aureus'* ability to cause clinical disease in a susceptible host. These include toxins which act on cell membranes; exotoxins such as toxic shock syndrome toxin and enterotoxins; leukocidin, which mediates the destruction of phagocytes; and catalases, coagulases, and hyaluronidases, which promote invasion and survival in tissue. Of particular interest is the Panton Valentine leukocidin (PVL) gene, which encodes for release of a cytotoxin responsible for tissue necrosis and leukocyte destruction. The presence of this gene has been associated with infections of greater severity [8]. *S. aureus* is a common colonizer of human skin and mucosa. It preferentially colonizes the anterior nares, particularly in adults, and at any given time 10–40% of the population is transiently colonized with the organism. A small proportion may become chronically colonized with *S. aureus* and, as such, is often at increased risk for clinical disease.

The discovery of penicillin proved to be extremely valuable in the treatment of infections due to staphylococci; however, resistance to this agent developed rapidly. Currently, susceptibility rates to penicillin are in single digits and thus, use of synthetic penicillins has become commonplace since the development of methicillin in the 1960s. Unfortunately, development of methicillin resistance among *S. aureus* was detected within months of its release. Resistance to methicillin develops once *S. aureus* acquires a large mobile genetic element, the staphylococcal cassette chromosome *mec* (SCC*mec*). Within this cassette the genes *ccrA* and *ccrB* mediate mobilization, and the *mec*A gene mediates β-lactam resistance. Specifically, *mec*A

encodes for an altered penicillin-binding protein, PBP2a. This protein, when found on the surface of the bacteria, has little affinity for β-lactam antibiotics and confers resistance to the entire class. Additionally, the *mec*A gene is often flanked by IS431, an insertion sequence that acts as a "collector" for additional antibiotic-resistance genes, thus promoting multidrug-resistant strains of MRSA. At least five different varieties of the SCC*mec* have been described (types I–V), based largely upon their corresponding *mec*A genes. Types I–III are large in size and tend to carry multiple antibiotic-resistance encoding genes. Types IV and V are smaller in size, are likely more mobile, and contain fewer antibiotic-resistance encoding genes. *S. aureus* resistant to methicillin has been defined in the laboratory as isolates with an MIC of $\geq$ 16 mg/L to methicillin or an MIC of $\geq$ 4 mg/L to oxacillin; however, more rapid and often more dependable methods for laboratory identification of methicillin resistance are those that actually detect the *mec*A gene, or the product of the gene, PBP2a.

MRSA has traditionally been considered an organism acquired within the healthcare system, but over the past several years, an increasing number of reports have described MRSA occurring among patients without this history. This emerging epidemiology has led many to describe MRSA as either healthcare-associated or community-associated, and the prevalence, resistance patterns, and clinical syndromes associated with the organism depend on this classification.

3.1 Healthcare-Associated MRSA

MRSA may be defined as healthcare-associated using a time-based definition such as being isolated from a patient after at least 72 h of admission to a healthcare facility. Additionally, healthcare-associated strains of MRSA tend to harbor the SCC*mec* types I, II, or III and are therefore usually multidrug-resistant. MRSA among hospitalized patients continues to be isolated with increased frequency and is an important cause of hospital-acquired infections. These infections include pneumonia (including ventilator-associated pneumonia), device-associated infections such as central-line associated bacteremia, and surgical site infections. According to data collected from US hospitals, the proportion of hospital-acquired infections due to *S. aureus* that were resistant to methicillin has continued to increase over the past two decades, and in 2004 approached 60% among ICU patients [9]. Experts suggest that evolutionary changes in the microorganism, combined with ineffective (or noncompliance with) infection-control measures and selective pressure from antibiotic use have all likely contributed to the continued rise of MRSA.

Risk factors for acquisition of healthcare-associated MRSA include prolonged hospital stay, particularly those in ICUs; exposure to and prolonged use of antibiotics; presence of severe underlying illness; receipt of invasive Procedures or foreign bodies; and being in close proximity to other MRSA-colonized or infected patients. Spread of MRSA in hospitals is thought to be largely due to patient-to-patient transmission from the contaminated equipment and hands of healthcare providers. MRSA is important because when patients develop infection due to the organism,

they suffer increased morbidity, mortality, and greater hospital costs than those who develop infection due to susceptible strains of the organism [10, 11]. A meta-analysis of studies of patients with *S. aureus* bacteremia reported that those with MRSA died almost twice as often, compared to those with methicillin-susceptible *S. aureus* [10], and another study of patients with *S. aureus* surgical site infections found that those with MRSA died more than three times as often, compared to those with methicillin-susceptible *S. aureus*, and had a 1.9-fold increase in hospital costs [11].

4 Community-Associated MRSA

MRSA may also be defined as community-associated, using the time-based approach described above, such as if the organism is isolated from a patient at the time of admission or within 48–72 h of admission to the hospital. Additionally, one may classify MRSA as community-associated if it is isolated from a patient presenting in the outpatient clinical setting or emergency department. Community-associated strains of MRSA usually harbor SCC*mec* IV and, less often, SCC*mec* V, and thus may retain some susceptibility to other classes of antibiotics. Also of note, MRSA isolates of community origin are more likely to possess the gene responsible for encoding PVL, a recognized virulence factor, and are often identified as the USA 300 clone when subjected to pulsed-field gel electrophoresis. Recent studies have described the frequency with which CA-MRSA has been occurring, as well as important characteristics among individuals with infections due to the organism [12, 13]. A study of patients with MRSA infections from Baltimore, Atlanta, and Minnesota reported that from 2001 through 2002, 8–20% of the MRSA isolates were classified as community-associated. The annual incidence of CA-MRSA disease was significantly higher among those less than 2 years old, and sometimes among blacks. Furthermore, the majority of infections (77%) were skin or soft tissue, but 6% were invasive in nature (e.g., bacteremias) and almost a quarter of patients with CA-MRSA infections required hospitalization. Also of interest was that among patients with CA-MRSA, many had contact with the healthcare system, such as visiting their physician within the previous year, or receiving antimicrobial therapy [12]. Another recent study documented that MRSA was the single most common identifiable cause of skin and soft-tissue infections among patients presenting to emergency departments in 11 US cities. The overall prevalence of MRSA was 59% and, among those, 97% were the USA 300 clone and 98% harbored SCC*mec* IV and were PVL positive [13]. Even though the majority of infections due to CA-MRSA have involved skin and soft tissue, the organism may also be a cause of more invasive infections, such as necrotizing fasciitis, bacteremia, or necrotizing pneumonia.

An important study was recently published and was the first to document the incidence and characteristics of invasive MRSA infections in nine US cities [14]. This population-based active case-finding study reported that, in 2005, more than 94,000 invasive MRSA infections occurred, for an estimated incidence rate

of 31.8 per 100,000 persons. These infections were associated with more than 18,000 deaths, for an estimated mortality rate of 6.3 per 100,000 persons. There was geographic variability, but in general most invasive MRSA infections were healthcare-associated; 58.4% were healthcare-associated community-onset infections and 26.6% were healthcare-associated hospital-onset infections. Only 13.7% of invasive MRSA infections were community-associated. Additionally, molecular analysis provided evidence that strains of community origin do cause a measurable amount of hospital-onset disease and in fact, 16% of invasive hospital-onset MRSA infections were due to the USA 300 clone [14].

Treatment for serious infections due to MRSA had been somewhat limited to agents such as vancomycin; however, newer agents with activity against the organism are now available. Vancomycin therapy requires an intravenous route, as well as monitoring of blood levels in order to assure adequate dosing and to avoid potential toxicity. Daptomycin, also given intravenously, is indicated for use in MRSA- and MSSA-complicated skin infections (at 4 mg/kg daily dose) and bacteremia, including right-sided endocarditis (at 6 mg/kg daily dose). Daptomycin levels do not need to be monitored; however, patients receiving the drug should be followed for the onset of muscle pain or weakness and weekly CPK levels should be measured. Another recently released intravenous agent with activity against MRSA is tygecycline. Regarding MRSA, this agent has clinical indications only for treatment of complicated skin and skin-structure infections at an initial dose of 100 mg, followed by 50 mg every 12 h. Linezolid, which can be given orally, has demonstrated pathogen-eradication rates and clinical efficacy comparable to that of vancomycin for commonly encountered infections, including skin and soft-tissue infections [15], and it may be associated with a more favorable outcome when used for treatment of MRSA nosocomial pneumonia (including ventilator-associated pneumonia) [16]. Additionally, older agents such as trimethoprim-sulfamethoxazole, clindamycin, and often tetracyclines may have activity and are often used for outpatient management of CA-MRSA infections, particularly those involving the skin and soft tissue.

5 Vancomycin-Intermediate *Staphylococcus aureus* and Vancomycin-Resistant *Staphylococcus aureus*

The past decade has seen first the emergence of *S. aureus* with intermediate resistance to and later frank resistance to vancomycin. Vancomycin-intermediate *S. aureus* (VISA) is defined in the microbiology lab as having an MIC toward vancomycin of 8–16 mg/L and has been described as a cause of infection primarily among patients on hemodialysis receiving long courses of vancomycin for MRSA infections [17]. The mechanism of resistance has been described as due to cell-wall thickening, which may cause the large vancomycin molecule to become trapped and unable to reach its functional targets. Vancomycin-resistant *S. aureus* (VRSA) is defined in the microbiology lab as having an MIC toward vancomycin of $\geq$64 mg/L. The mechanism of resistance for this extremely worrisome pathogen is acquisition

of the *vanA* gene from vancomycin-resistant *Enterococcus* (VRE). Emergence of this organism has originated in areas where MRSA and VRE have co-existed, and at least seven cases have been described in the United States [18]. Fortunately, these VISA and VRSA strains have retained susceptibility to many alternative antibiotic agents, but their mere existence highlights the importance of controlling their spread in healthcare facilities.

6 *Enterococcus* Species

Enterococcus, a resident normal flora of the gastrointestinal and genitourinary tract, was once classified as a group D *streptococcus*; however, advancements in nucleic acid analysis revealed that enterococci were not closely related to streptococci and a new genus was proposed [19]. Enterococci are facultative anaerobic organisms that grow at extreme temperatures and hydrolyze esculin in the presence of bile. Once thought to be of insignificant consequence to humans, *Enterococcus* is now the second- to third-most common cause of nosocomial infections in US hospitals and two species, *Enterococcus faecalis* and *E. faecium,* cause 90% of these infections.

Enterococci exhibit intrinsic resistance of varying degrees to many antibiotics traditionally used to treat infections due to gram-positive pathogens. Enterococci are much less susceptible to β-lactams than streptococci. For Example, *E. faecalis'* MIC toward ampicillin is 1 μg/mL, and its MIC toward penicillin and piperacillin is 2 μg/mL. Additionally, the cephalosporins are essentially ineffective against enterococci. Intrinsic resistance to β-lactams results from the reduced affinity of the penicillin-binding protein of the organism. Also of note, even if enterococci are susceptible to penicillins, if they are exposed to this class of antibiotics, they may develop tolerance to the drug's killing effect [19]. Acquired resistance among enterococci is an additional concern, particularly toward the aminoglycosides (streptomycin and gentamicin) and toward the glycopeptide, vancomycin. The most common and best described mechanism for enterococci to become resistant to vancomycin is by acquisition of the *vanA* gene cluster found on the transposable genetic element Tn*1546*. When enterococci possess this gene cluster and are exposed to vancomycin, they produce the enzymes necessary to cross-link peptides with altered terminal sequences (D-Ala-D-lactate instead of D-Ala-D-Ala). These altered sites have much less affinity for binding glycopeptides.

Unfortunately, just as we have seen the continued increase in other antibiotic-resistant organisms, VRE has followed suit. Data from US hospitals suggest that the prevalence of enterococci causing nosocomial infections that were vancomycin-resistant has continued to increase over the past decade and now has surpassed 30% among ICU patients [9]. Emergence of the organism in the healthcare system has been facilitated by the overuse of broad-spectrum antibiotics. Patients acquire colonization or infection and subsequently contaminate their hospital environment with this hardy organism. Just as is the case for other resistant organisms, such as MRSA, spread from patient to patient occurs almost always by contaminated hands and equipment of healthcare workers. Risk factors for VRE acquisition have

been described and include the presence of an underlying co-morbid condition such as diabetes, renal failure, or malignancy; lengthy hospital stay; receipt of broad-spectrum antibiotics such as cephalosporins and vancomycin; having indwelling devices; and being in close proximity to another VRE-colonized or infected patient. VRE colonization increases the risk of VRE infection. The most common site of infection has been described as the urinary tract (cystitis, pyelonephritis, prostatitis), but more invasive infections occur, such as bloodstream infections and endocarditis.

The continued increase in VRE is concerning because patients who develop infection with VRE suffer increased morbidity, mortality, and greater hospital costs than those who develop infection caused by vancomycin-susceptible *Enterococcus* (VSE).

A large retrospective-matched case–control study comparing patients with VRE bloodstream infections to those with VSE bloodstream infections reported that those with VRE had significantly greater mortality (RR 2.13, 95% CI 1.05–4.37); greater length of stay (RR 1.73, 95% CI 1.43–2.10); greater mean cost (RR 1.40, 95% CI 1.26–1.59); greater need for surgery (RR 2.74, 95% CI 1.52–4.92); greater need for ICU admission (RR 3.47, 95% CI 1.75–6.85); and greater need to be discharged to a long-term care facility (RR 2.01, 95% CI 1.34–3.02) [20]. Additionally, data from multiple studies comparing patients with VRE bloodstream infection to those with VSE bloodstream infection suggest that VRE bacteremia has been associated with higher rates of recurrent BSI (16.9% vs. 3.7%, $p<0.0001$); higher crude case fatality rates (RR=2.57, 95% CI = 2.27–2.91); higher mortality due to bacteremia (RR = 1.79, 95% CI = 1.28–2.50); and greater hospital costs of $27,000 per episode of bloodstream infection ($p = 0.04$) [21].

The treatment of infections due to vancomycin-resistant strains of *Enterococcus* is a challenge because there are a limited number of agents available with sufficient activity against the organism and fewer agents have actually been studied in clinical trials. Quinupristin-dalfopristin has activity against *E. faecium*, but not most strains of *E. faecalis*. This, accompanied by the fact that it has significant side effects and must be given through a central venous catheter, significantly limits its use. Linezolid has activity against VRE [22], but this drug is bacteriostatic and thus must be used with caution among patients with bacteremia or endocarditis where bactericidal therapy is preferred. Linezolid is also associated with myelosuppression and thus is not typically considered a good choice for infections where long-term therapy (i.e., greater than 2 weeks) is needed. Daptomycin is bactericidal against VRE and may be considered for these more invasive infections; however, there are no comparative clinical studies specifically directed toward its use against VRE. Additionally, some strains of *E. faecium* have higher MICs toward daptomycin. Tigecycline has in vitro activity against VRE and has been studied for complicated skin and soft-tissue infections and intra-abdominal infections where VRE was isolated, but there is no formal indication for use of this drug for VRE infections [23]. Thus, each patient must be approached individually and much must be taken into consideration, such as type of infection and ability to remove foreign bodies or drain areas of infection, as well as underlying host factors. For patients with VRE infections with MICs to ampicillin ranging between 16 and 64 μg/mL, high doses of the drug may

be used (24 g a day divided q4h) plus gentamicin or streptomycin for severe invasive infections such as endocarditis. For invasive disease due to ampicillin-resistant VRE, off-label use of daptomycin or tigecycline should be considered. For endocarditis, these agents should be used in combination with another agent, based upon susceptibilities. These normally would include gentamicin or streptomycin; however, in vitro data support the use of doxycycline, rifampin, imipenem, or a fluoroquinolone.

7 Conclusion

Antibiotic resistance among gram-positive organisms continues to be a growing concern. Patients who acquire invasive infections due to these pathogens often stay sicker longer, have excess costs associated with their care, and more importantly, have increased risk of mortality. Treatment options are often limited for infections due to resistant gram positives and thus, efforts expended for control are needed.

Reducing the use of unnecessary antibiotics, particularly in the outpatient setting, coupled with vaccination efforts, will be important if the emergence of resistant *S. pneumo* is to be halted. Additionally, guidelines exist regarding control of antibiotic-resistant organisms, such as MRSA and VRE, and include reducing emergence of the organism by antibiotic control or effective stewardship, reducing patient-to-patient spread by reducing contamination of the environment (disinfection, terminal cleaning, dedicated pt equipment), and reducing contamination of the healthcare worker (hand hygiene, gowns, and gloves). Additionally, healthcare-acquired infections can be effectively controlled by closely following institutional infection-control measures, as well as published prevention guidelines for central venous catheter-associated bloodstream infections and ventilator-associated pneumonia.

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Gram-Negative Bacteria

Craig A. Martin

1 Introduction

Gram-negative bacteria are important causes of infection in institutionalized as well as community-dwelling patients. Urinary tract infections (UTI), otitis media (OM), sexually transmitted diseases (STD), acute and chronic bronchitis, and community-acquired pneumonia (CAP) are among the infections often caused by gram-negative organisms in ambulatory settings. Gram-negative pathogens commonly seen in primary care include *Escherichia coli* (UTI); *Haemophilus influenzae* (CAP and bronchitis); *Klebsiella pneumoniae* (CAP and UTI); *Neisseria gonorrhoeae* (gonorrhea), and *Neisseria meningitidis* (meningitis). Each of these pathogens presents the clinician with unique challenges, including awareness and management of antimicrobial resistance. Historically, healthcare providers have considered bacterial resistance a hospital dilemma with little impact on ambulatory patients. Without question, inpatient facilities are areas of concentration for resistance, but several factors have forced practitioners in all settings to become familiar with these issues. Increasing antimicrobial use in the community, a relative shortage of new antimicrobials with novel mechanisms of action, and increases in outpatient therapy for many diseases have forced resistance issues into the ambulatory setting. Proper diagnosis, responsible antimicrobial use, and familiarity with local resistance patterns can help equip the clinician with the tools needed to treat patients adequately, while avoiding antimicrobial collateral damage.

The cell wall of gram-negative bacteria differs significantly from its gram-positive counterpart. The peptidoglycan layer, while thick in gram-positives, is thin in gram-negatives and lies beneath a bilayer consisting of lipopolysaccharide and other macromolecules. Due to the lipophilicity of the bilayer, water-soluble substances (such as antimicrobials) are unable to diffuse into the cell. Instead, these agents must gain access to their sites of action through water-filled porins. These

C.A. Martin (✉)
Department of Pharmacy Practice and Science, UK HealthCare, University of Kentucky, Lexington, KY, USA
e-mail: cmart2@email.uky.edu

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Table 1 Examples of resistance mechanisms in gram-negative bacteria

General resistance category	Specific Examples
Production of enzymes that alter antimicrobial structure	Beta-lactamases; aminoglycoside-modifying enzymes
Cell wall impermeability	Porin channel deletions mediating imipenem resistance; Enterobacteriaceae resistance to penicillin
Target-site modification	Changes in DNA gyrase and topoisomerase IV (fluoroquinolone resistance); methylation of ribosome (macrolide and clindamycin resistance)
Efflux pump mediated elimination of drug from cell	Fluoroquinolone resistance in *E. coli*

selective channels allow certain ions and molecules to gain entry into the cell and are relatively discriminating. If an antimicrobial agent is unable to gain entry into the cell through this route, it will be ineffective in eradicating the organism.

Over the past several years, resistance to antimicrobial agents commonly used to treat gram-negative pathogens has increased dramatically. Examples of resistance mechanisms common to gram-negative bacteria are listed in Table 1. *Pseudomonas aeruginosa, Acinetobacter baumannii,* and *K. pneumoniae* are among the most common of the so-called multidrug-resistant (MDR) bacteria. Excessive use of antimicrobials, infection control indiscretions, and plasmid-mediated resistance gene transfer all play important roles in this emerging threat. Reports of gram-negative pathogens resistant to all – or nearly all – commonly used antimicrobial agents have become increasingly commonplace, both in the United States and abroad. As a true example of the amazing genetic adaptability of these organisms, *P. aeruginosa* often combines multiple mechanisms to result in broad-spectrum resistance [1]. In what has been described as a public health crisis, perilously few novel antimicrobial agents are in development for the treatment of MDR gram-negative pathogens [2]. Efforts to preserve the current antimicrobial arsenal are crucial to future success in treating gram-negative infections.

2 Beta-Lactam Antibiotics: Activity and Resistance

The gram-negative activity of penicillin agents typically increases as one goes from penicillin to ampicillin to ticarcillin to piperacillin (Table 2). Generally speaking, the gram-negative spectrum of penicillin G is limited to *Neisseria* spp. Even then, beta-lactamase production in *N. gonorrhoeae* has become common, limiting the usefulness of penicillin G for the treatment of gonorrhea. The addition of an amino group (such as with ampicillin and amoxicillin) allows entry through the porin channels and expands the gram-negative spectrum to include efficacy against such pathogens as *E. coli*, *Proteus mirabilis*, and *H. influenzae*, among others. It should be noted that this enhanced gram-negative spectrum does not include specific

Table 2 Penicillin agent subtypes and activity

Subtype	Representative(s)	Gram-negative spectrum examples	Notes
Penicillin	Penicillin G	*Neisseria gonorrhoeae; Neisseria meningitidis*	Beta-lactamase (–) strains only
Aminopenicillin	Amoxicillin; ampicillin	As above + *Escherichia coli; Proteus mirabilis; Haemophilus influenzae*	Beta-lactamase (–) strains only
Carboxypenicillin	Ticarcillin	As above + *Pseudomonas aeruginosa*; *Enterobacter* spp.; *Acinetobacter* spp.; *Serratia* spp.; other Enterobacteriaceae	Improved stability to certain beta-lactamases
Ureidopenicillin	Piperacillin	As above	As above
Beta-lactamase inhibitors	Amoxicillin/ clavulanate; ampicillin/ sulbactam; ticarcillin/ clavulanate; piperacillin/ tazobactam	Activity of parent compound (including many beta-lactamase producers) + anaerobes (*Bacteroides fragilis* and others)	Addition of beta-lactamase inhibitor may restore activity of parent compound in the face of beta-lactamase production

strains that produce beta-lactamases, as amoxicillin and ampicillin have no protection against such enzymes. The carboxypenicillin ticarcillin is afforded an expanded gram-negative spectrum, owing its relative stability to the beta-lactamases produced by *P. aeruginosa* and *Enterobacter* spp. Piperacillin, a ureidopenicillin, also has significant activity against such pathogens [3].

Like penicillins, cephalosporins vary significantly in their gram-negative activity. First-generation agents such as cefazolin are active against important pathogens like *E. coli* and *K. pneumoniae*. This spectrum includes those isolates that produce narrow-spectrum beta-lactamases. Third-generation agents, including ceftazidime, cefotaxime, and ceftriaxone, and the fourth-generation agent cefepime exhibit significantly greater potency against these pathogens. In addition, these extended-spectrum cephalosporins possess activity against *Enterobacter* spp.; *Citrobacter* spp.; *Serratia* spp.; *Salmonella* spp.; *Shigella* spp.; and *Acinetobacter* spp. Ceftazidime and cefepime also have activity against *P. aeruginosa*. Mutational resistance is common in these pathogens and is discussed later [4].

Aztreonam is currently the only marketed agent from the class of drugs called the monobactams – a subgroup of beta-lactam antimicrobials. The spectrum of activity of aztreonam is limited to aerobic gram-negative bacteria and includes nearly all clinically relevant bacteria of this classification. Aztreonam is most often used for patients in whom beta-lactam therapy is desired, but who have serious allergies to other beta-lactam drugs. The risk of cross-sensitivity between aztreonam and other beta-lactams is negligible [5].

The group of beta-lactam agents known as the carbapenems has, in many cases, become the usual last line of defense against MDR gram-negative bacteria. These agents have a spectrum of activity that encompasses nearly all gram-negative pathogens, and resistance is notably less common than with other beta-lactams, owing to the fact that most beta-lactamases do not hydrolyze them. Imipenem, meropenem, and doripenem have significant activity against *P. aeruginosa*; however, ertapenem does not. Mutational resistance to the carbapenems has become a significant problem in many locales, typically in areas where widespread use occurs [5].

Among the most common mechanisms of resistance in gram-negative pathogens is the production of beta-lactamases. These hydrolytic enzymes result in the degradation of beta-lactam antimicrobials (penicillins, cephalosporins, aztreonam, and carbapenems). Because of the heterogeneity of these enzymes, several classification schemes have been proposed. Table 3 illustrates the classification system developed by Bush, Jacoby, and Medeiros (BJM) [6]. It should be noted that several attempts to produce antimicrobial agents with stability to these beta-lactamases

Table 3 Classification of beta-lactamases by Bush, Jacoby, and Medeiros (BJM) [6]

Class	Representative bacteria	Beta-lactams affected	Beta-lactams not affected
I	*Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Acinetobacter baumannii*	Penicillins, cephalosporins, aztreonam	Carbapenems
IIa	*Staphylococcus aureus*	Penicillins	Cephalosporins, carbapenems
IIb	*Escherichia coli*, *Klebsiella pneumoniae*, many gram-negative bacteria	Penicillins	Cephalosporins, carbapenems, aztreonam
IIbe (ESBLs)	*Escherichia coli*, *Klebsiella pneumoniae*, many gram-negative bacteria	Penicillins, cephalosporins, aztreonam	Carbapenems
IIf (KPCs)	*Klebsiella pneumoniae*	Penicillins, cephalosporins, aztreonam, carbapenems	
III (MBLs)	*Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*	Penicillins, cephalosporins, carbapenems	Aztreonam (clinical utility unknown)

have been undertaken, with some success. While the early penicillins – penicillin and ampicillin – do not exhibit stability to beta-lactamases, the extended-spectrum penicillins; beta-lactamase inhibitor combination agents; cephalosporins; carbapenems; and aztreonam all possess varying degrees of stability to beta-lactamases, a characteristic that is highly dependent on the specific beta-lactamase in question.

Despite advances in drug discovery for agents active against beta-lactamase-producing gram-negative bacteria, pinpoint mutations in genes mediating beta-lactamase production can extend the activity of the parent enzyme and have given rise to extended-spectrum beta-lactamases (ESBLs). The ESBLs were identified and have proliferated in the time period following the Introduction of oxyiminocephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone). These enzymes are most commonly seen in *E. coli* and *Klebsiella* spp., but have recently proliferated in other gram-negative bacteria as well. In clinical settings where oxyiminocephalosporins are heavily utilized, ESBL-producing gram-negative bacteria become commonplace. Attempts to control ESBL production by decreasing the use of these agents are often successful but may carry other consequences, a phenomenon known as "squeezing the resistance balloon" [7]. The key to controlling ESBL production is prevention through prudent antimicrobial use, especially of oxyiminocephalosporins.

Laboratory identification of ESBL-producing organisms is difficult, again due to the heterogeneity of the enzymes in question. Most clinical isolates producing ESBLs will initially test "resistant" to multiple beta-lactams, including third-generation cephalosporins. In some, however, the bacteria may not have a minimum inhibitory concentration (MIC) to third-generation cephalosporins high enough to garner this classification. Given the inability of Clinical Laboratory Standards Institute (CLSI; formerly NCCLS) breakpoints to predict efficacy in "susceptible" ESBL producers, identification of these bacteria is of paramount importance. CLSI has introduced a screening method to identify and confirm suspected ESBLs in isolates with elevated MICs, but the method is currently only validated and approved for *E. coli*, *Klebsiella* spp., and *P. mirabilis*. Clinical microbiology laboratories have little guidance on the identification of ESBLs in other gram-negative bacteria [8]. One method for detecting ESBLs (E-test®) is depicted in Fig. 1.

According to CLSI, when Enterobacteriaceae-harboring ESBLs are identified, the laboratory must report the isolate as "resistant" to all penicillins, cephalosporins, and aztreonam. This is an important point, as not all ESBL-producing bacteria will test as overtly resistant to all of these agents. In these cases, however, the appearance of in vitro susceptibility is false and fails to predict reliably in vivo success [9]. Beta-lactamase inhibitor combinations (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, and ticarcillin/clavulanate) may have varying degrees of in vitro activity, but their clinical utility in patients infected with these organisms remains questionable. Thus, these agents cannot be routinely recommended for ESBL-producing bacteria. Carbapenems (imipenem, meropenem, ertapenem, and doripenem) typically become the drugs of choice, as fluoroquinolone co-resistance

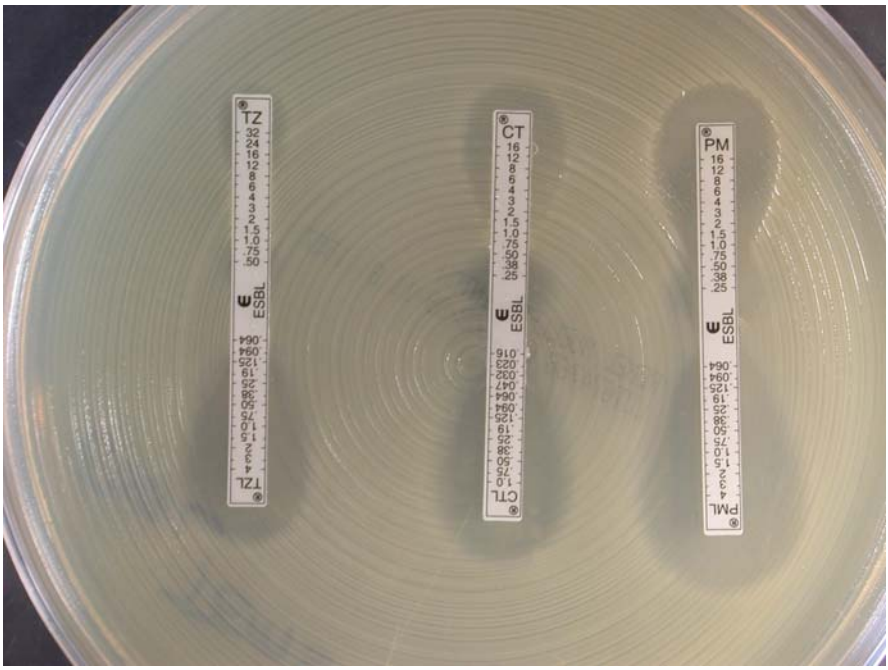

Fig. 1 Example of the E-test® method to confirming ESBL production in gram negative bacteria. The addition of the beta-lactamase inhibitor (lower portion of each strip) to the beta-lactam (upper portion) restores much of the activity of the drug, as noted by the larger zones of inhibition. Photo courtesy of Dr. Julia Ribes, University of Kentucky

is common and aminoglycosides are not often recommended for monotherapy. A newer glycylcycline agent, tigecycline, may prove to have some benefit in this area, but the exact place in therapy for this agent is still being elucidated.

Some Enterobacteriaceae (e.g., *Enterobacter* spp.), as well as *P. aeruginosa* and *Acinetobacter* spp., have long been known to produce a beta-lactamase (BJM class I, Table 3) mediated by the gene called ampC. Under normal circumstances, this beta-lactamase is subject to tight control by accessory genes and is mostly produced as a protective mechanism for the bacteria when exposed to beta-lactam agents. Under special circumstances – through mutation in those accessory genes – the production of this beta-lactamase is unabated. Some beta-lactam agents may preferentially select these resistant mutants through their activity against the susceptible majority. As the resistant minority proliferates, overall beta-lactamase production increases, and the risk for treatment-emergent resistance follows. The risk of clinical failure in *Enterobacter* spp. bacteremia upon treatment with a third-generation cephalosporin is as high as 20–30% [10]. This phenomenon has been called "ampC hyperproduction," as well as "stable derepression." The resulting high level of enzyme

production mediates resistance to penicillins, most cephalosporins, and aztreonam. Cefepime may continue to demonstrate in vitro activity, but its clinical utility in these cases remains largely unproven. Notably, the beta-lactamase inhibitors (clavulanate, sulbactam, and tazobactam) have no significant inhibitory activity against these enzymes. As with ESBLs, the drugs of choice often become carbapenems, due to the large database of clinical utility with these agents. Other agents, such as fluoroquinolones, aminoglycosides, and tigecycline, may also provide some benefit depending on individual susceptibilities [8].

Metallo-beta-lactamases (MBLs) have emerged in recent years and represent an especially concerning resistance trend. These molecules are so named because they rely on a high concentration of zinc within the enzyme to interact with the beta-lactam (most other beta-lactamases rely on high serine concentrations). It has been known for quite sometime that certain gram-negative bacteria – most notably *Stenotrophomonas maltophilia* – are common producers of these enzymes, which are included in BJM class III (Table 3). The most concerning aspect of these enzymes is their broad spectrum of hydrolysis, which includes penicillins, cephalosporins, and notably the carbapenems. For this reason, MBLs are also classified as "carbapenemases." Organisms producing these enzymes have proliferated in some geographic areas, typically those in which carbapenem consumption is high. They have also become more common in organisms other than those that have historically produced MBLs. *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, and *Enterobacter* spp. are among the organisms found to produce MBLs [10]. Given the broad scope of resistance that accompanies this mechanism of resistance, antimicrobial therapy with an agent outside the beta-lactam family is required.

Fairly recently, researchers and clinicians have noted an increase in organisms that produce beta-lactamases known as KPCs (*Klebsiella pneumoniae carbapenemase*), which are members of BJM class II (Table 3). First discovered in *K. pneumoniae* in 1996, these beta-lactamases are plasmid-mediated and confer resistance to penicillins, cephalosporins, and carbapenems. Quickly after the first isolation of KPC-1 in *K. pneumoniae*, KPC-2 and KPC-3 – amino acid variants of KPC-1 – were detected in the United States and in other parts of the world. Currently, *K. pneumoniae* is the predominant producer of KPC enzymes, but *Enterobacter* spp., *E. coli*, and *Salmonella* spp. have also been found to harbor KPC enzymes.

As with MBLs, the proliferation of KPCs seems to cluster in areas of high carbapenem usage. The best Example of this is the New York metropolitan area, where carbapenem use has often been necessitated by outbreaks of ESBL-producing *K. pneumoniae*. In response to this increased carbapenem use, *K. pneumoniae* that produce KPC-2 have become common. In the setting of infection with this type of MDR organism, treatment options are limited. Tigecycline, polymyxin B, polymyxin E (colistin), and other non-beta-lactam agents often become the drugs of choice, but each has its limitations.

3 Fluoroquinolones: Activity and Resistance

Fluoroquinolones have become commonly used agents in ambulatory settings for a broad range of infections including UTIs, pneumonia and other respiratory infections, and gastrointestinal infections, among others. Their rapidly expanding use in the community is due to a variety of factors. They are relatively safe compounds with high bioavailability, making oral dosing for moderate infections reasonable. While they have been shown to be effective for a multitude of indications, their increasing use has been associated with increasing resistance in key pathogens. Fluoroquinolones have varying degrees of gram-negative activity. Ciprofloxacin and levofloxacin exhibit the broadest activity, including most Enterobacteriaceae, *Acinetobacter* spp., and *P. aeruginosa*, among others. The clinician should observe caution when using fluoroquinolones to treat infections caused by *P. aeruginosa*, as resistance occurs frequently. For this reason, if *P. aeruginosa* is the suspected or confirmed pathogen in a serious infection (other than UTI) it is prudent to avoid monotherapy with a fluoroquinolone, and only use these agents as part of a combination. Urinary tract infection may represent an exception to this rule for ciprofloxacin and levofloxacin, given their ability to concentrate in urine. Moxifloxacin possesses moderate gram-negative activity, with a spectrum that includes most Enterobacteriaceae, but not *P. aeruginosa*. Gemifloxacin has significantly less gram-negative activity than its counterparts.

Resistance to fluoroquinolones in gram-negative bacteria has been increasing recently. Alterations in DNA gyrase and topoisomerase IV – the fluoroquinolone targets – constitute much of this mutational resistance. The presence of multidrug efflux pumps – pumps that remove the drug before its antimicrobial action can be achieved, which is seen especially in *P. aeruginosa* – has emerged as a significant contributor to fluoroquinolone resistance as well.

4 Aminoglycosides: Activity and Resistance

Aminoglycosides remain among the most commonly used antimicrobial agents for the treatment of infections caused by gram-negative pathogens, typically in combination with other agents. Gentamicin, tobramycin, and amikacin are the agents typically used for the treatment of gram-negative infections. Their spectrum of activity includes Enterobacteriaceae, *Acinetobacter* spp., and *P. aeruginosa*. They exhibit concentration-dependent bactericidal action by binding to the 30S ribosomal subunit and preventing bacterial protein synthesis.

Intrinsic aminoglycoside resistance occurs mostly via drug exclusion from the cell. Anaerobic bacteria are intrinsically resistant to aminoglycosides through this mechanism. Several other mechanisms of resistance have been identified, including multidrug efflux pumps, target-site modification at the level of the ribosome, and enzymes that destroy the aminoglycoside molecule (aminoglycoside-modifying enzymes). Clinically, gentamicin and tobramycin are more often affected by aminoglycoside-modifying enzymes than amikacin.

5 Gram-Negative Organisms

5.1 Escherichia coli

E. coli is among the most common gram-negative pathogens encountered in clinical practice. A part of the normal human gastrointestinal flora, *E. coli* is the primary cause of urinary tract infections (UTIs) in the outpatient setting. Infections caused by this pathogen, however, range from uncomplicated UTIs to hospital-acquired pneumonia and sepsis. For this reason, antimicrobial resistance in *E. coli* is of significant import in both the ambulatory and hospitalized patient.

Inexpensive and generally effective, sulfamethoxazole/trimethoprim (SMZ/TMP) is a mainstay of therapy for UTIs in the ambulatory setting. Historically, resistance to SMZ/TMP in *E. coli* has remained fairly low. In recent years, however, resistance has been increasing (near or above 20% in some locales), and clinical failures have been reported [11]. As a result, clinicians are faced with a difficult quandary – whether or not to continue using SMZ/TMP empirically for the treatment of UTIs. On one hand, clinical failure rates, even in the setting of up to 20% resistance, remain relatively low. On the other hand, investigators have suggested that when resistance rates exceed 20%, SMZ/TMP becomes less cost-effective than fluoroquinolone therapy because of the increased rate of treatment failure and resource utilization. These recommendations do not take into account increasing rates of fluoroquinolone resistance.

E. coli is a common producer of beta-lactamases, most often those of BJM functional group II. The typical beta-lactamase produced by *E. coli* clinical isolates is a narrow-spectrum enzyme (TEM-1) with hydrolytic activity limited to the unprotected penicillin agents (e.g., ampicillin, amoxicillin, etc.). This enzyme is plasmid-mediated and, therefore, can be transferred to or from other bacteria through gene transfer. In an isolate without beta-lactamase production, the inclusion of an amino group on the penicillin core affords ampicillin and amoxicillin – the so-called aminopenicillins – significant antimicrobial activity against *E. coli*. In the presence of beta-lactamase, however, these agents are rendered ineffective. The addition of a beta-lactamase inhibitor to amoxicillin (clavulanate), ampicillin (sulbactam), ticarcillin (clavulanate), or piperacillin (tazobactam) restores the activity of the agent. Other beta-lactam agents, such as cephalosporins, aztreonam, and carbapenems, retain significant activity against *E. coli* strains that produce narrow-spectrum beta-lactamases such as TEM-1 and SHV-1.

As with some other gram-negative bacteria, pinpoint mutations in genes mediating beta-lactamase production can give rise to ESBLs. In fact, *E. coli* is among the most common ESBL-producing bacterium in clinical practice. In this setting, the clinician is advised to avoid all penicillins, cephalosporins, and aztreonam. Depending on the susceptibility to other agents outside the beta-lactam family, as well as the site of infection, carbapenems may be the therapy of choice.

Resistance to fluoroquinolones among clinical strains of *E. coli* has been on the rise in recent years. In 2004, according to the National Nosocomial Infections Surveillance (NNIS) project, nearly 10% of *E. coli* strains isolated from hospitalized patients were resistant to the fluoroquinolones [12]. In strains that also harbor

ESBLs, resistance rates are even higher and approach 50% in some reports [9]. Most commonly, this resistance is due either to efflux pumps or target-site modification. Ciprofloxacin and levofloxacin, along with some older fluoroquinolones such as ofloxacin and norfloxacin, are commonly used to treat complicated and uncomplicated UTIs, where *E. coli* is a common pathogen. As mentioned previously, clinicians are often faced with the choice of SMZ/TMP or a fluoroquinolone, for empiric treatment of UTIs. Fluoroquinolone resistance in *E. coli* makes this decision significantly more difficult. Culture and susceptibility data are important for choosing appropriate antimicrobial therapy.

5.2 Klebsiella pneumoniae

K. pneumoniae is a commonly encountered pathogen in clinical practice. In the community, it is associated with urinary tract infections and, less commonly, community-acquired pneumonia. In the hospital setting, *K. pneumoniae* causes several diverse infections, including hospital-acquired and ventilator-associated pneumonia; bacteremia; urinary tract infections; and intra-abdominal infections, among others. This broad scope of pathogenicity, along with its ability to harbor resistance mechanisms – either intrinsically or acquired – makes *K. pneumoniae* a formidable pathogen.

In contrast to *E. coli*, which may or may not produce a beta-lactamase, *K. pneumoniae* is a constant producer of SHV-1 (BJM class IIb). While ampicillin and amoxicillin could be expected to penetrate the cell wall of *K. pneumoniae*, they have no protection against beta-lactamases, precluding therapy with these agents. Even piperacillin and ticarcillin are subject to some hydrolysis by this enzyme. The addition of a beta-lactamase inhibitor (e.g., piperacillin/tazobactam, ticarcillin/clavulanate, ampicillin/sulbactam, or amoxicillin/clavulanate) should restore the efficacy of the penicillin agent, provided no ESBLs or other resistance mechanisms are present. Extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime, etc.), aztreonam, and carbapenems are also afforded stability to the SHV-1 enzyme and would therefore be reasonable treatment options for this type of isolate. Other non-beta-lactam agents can also be considered.

As with *E. coli*, emergence of ESBL-producing *K. pneumoniae* has increased along with the increasing use of oxyiminocephalosporins. According to the National Nosocomial Infections Surveillance (NNIS) system, *K. pneumoniae* resistance to ceftazidime in US intensive care units increased approximately 600% between 1988 and 2004 (this resistance can be seen as a surrogate for the presence of ESBLs) [12]. Given the multidrug resistance profile of ESBL-producing gram-negative bacteria, a reasonable assumption can be made that this increase has also occurred with respect to penicillins and aztreonam.

Fluoroquinolone resistance in *K. pneumoniae* is similar to that in *E. coli* and other Enterobacteriaceae, albeit at a low rate of occurrence. Resistance most commonly occurs as a mutation of DNA gyrase, with gyrA being the specific gene affected. Topoisomerase IV mutation (also a binding site alteration) also occurs, but is more often associated with gram-positive resistance than gram-negative resistance. Efflux

pumps are also known to mediate fluoroquinolone resistance in *K. pneumoniae*. Any one of these mutations may be enough to mediate resistance to the fluoroquinolones, but the combination of multiple mutations often Results in high-level resistance.

5.3 Pseudomonas aeruginosa

P. aeruginosa is the most common gram-negative bacteria causing hospital-acquired infections in critically ill patients. Even without the presence of mutational resistance, *P. aeruginosa* is inherently resistant to many agents, either through beta-lactamase production or through exclusion of antimicrobial agents from the cell [1]. Mutational resistance has been increasing in frequency as well. In 2004, the proportion of *P. aeruginosa* isolates resistant to ceftazidime and imipenem approached 25% [12]. Imipenem – along with the other antipseudomonal carbapenems, meropenem and doripenem – is often seen as the last line of therapy for resistant gram-negative infections, especially those caused by *P. aeruginosa*. In the setting of carbapenem resistance, clinicians may be forced to use polymyxin B or colistin – agents once thought of as too toxic for systemic use. Tigecycline can be a treatment option for other MDR gram-negative pathogens, but it exhibits poor in vitro activity against *P. aeruginosa*.

Beta-lactam resistance in *P. aeruginosa* can be due to a variety of mechanisms. First and foremost, *P. aeruginosa* is a producer of beta-lactamases, most often BJM class I (Table 3). Wild-type strains produce these enzymes in an inducible fashion. In this state, ticarcillin and piperacillin are not significantly affected. As mentioned previously, however, once these ampC-mediated enzymes become stably derepressed, they confer resistance to all penicillins, cephalosporins, and aztreonam and are not affected by beta-lactamase inhibitors. Other beta-lactamases have also been found in *P. aeruginosa*. Class II (including ESBLs) and class III (carbapenemases) have been reported and are increasing in frequency [1].

Antimicrobial efflux pumps are becoming more frequent in clinical isolates of *P. aeruginosa*. These pumps remove the antimicrobial from the cell before antimicrobial action can occur. Like cell wall impermeability, efflux pumps may be either drug-specific or have action on several agents. *P. aeruginosa* has been shown to harbor several efflux pumps, affecting antimicrobials ranging from fluoroquinolones and aminoglycosides to penicillins, cephalosporins, aztreonam, and carbapenems. In fact, upregulation of these pumps affects most beta-lactams. It should be noted that imipenem is the beta-lactam least affected by efflux-mediated resistance [1].

As mentioned previously, antimicrobials are reliant upon porin channels in the gram-negative cell wall in order to access their respective sites of action. One channel, OprD, is particularly subject to mutational downregulation. The loss of this porin channel significantly reduces the antibacterial effect of imipenem, as its entry into the cell is solely dependent on this route. Downregulation of OprD is a common mechanism of imipenem resistance in *P. aeruginosa*. Meropenem and doripenem can gain entry into the cell through alternative routes and are, therefore, less affected by OprD loss.

Throughout the 1990s and 2000s, *P. aeruginosa* became increasingly resistant to fluoroquinolones. As these agents have become more commonly used in clinical practice, resistance has followed [14]. In fact, 30–40% of clinical strains are now resistant to ciprofloxacin and levofloxacin, the only fluoroquinolones with significant *P. aeruginosa* activity. This resistance can be due to alterations in DNA gyrase and topoisomerase IV or to efflux pumps. Even those strains that remain susceptible are unlikely to be eradicated with either of these agents as monotherapy, as resistance often emerges during treatment. For these reasons, many clinicians will employ the combination of an antipseudomonal beta-lactam and an aminoglycoside for serious pseudomonal infections, reserving fluoroquinolones as an aminoglycoside substitute in patients who may be at risk for nephrotoxicity.

5.4 Acinetobacter baumannii

A. baumannii is a significant and emerging nosocomial pathogen, as well as a formidable cause of infections in soldiers who have been deployed in the Middle East. While the overall proportion of infections caused by *A. baumannii* remains lower than *P. aeruginosa*, its propensity for resistance is concerning. From 1986 to 2004, resistance in ICUs to ceftazidime increased in this pathogen from approximately 25 to nearly 70% [13]. Several outbreaks have been reported in which resistance to almost every available antimicrobial was seen [15]. Like *P. aeruginosa*, *Acinetobacter* produces an inducible BJM class I beta-lactamase that can become stably derepressed through mutation. This type of resistance negates the penicillins, cephalosporins, and aztreonam. Because co-resistance with fluoroquinolones and aminoglycosides is common, carbapenems become the agents most often used in this setting. Several epidemiological studies have been published outlining the effect of carbapenem overuse on the MDR profile of *A. baumannii* [7, 16]. In areas where carbapenem use is high, resistance to all beta-lactams can be seen, due to diverse beta-lactamase production (class I, II, or III), porin channel downregulation, efflux pumps, or a combination of these. Resistance to fluoroquinolones and aminoglycosides occurs through similar mechanisms as those seen in *P. aeruginosa*, with fluoroquinolone resistance occurring frequently. Unlike *P. aeruginosa*, ampicillin/sulbactam may provide a therapeutic alternative for MDR *A. baumannii* isolates.

Tigecycline, the first agent in a new class called glycylcyclines (derivatives of minocycline) may provide some therapeutic utility for MDR *Acinetobacter* infections. The spectrum of tigecycline is broad, but importantly, it does not include *P. aeruginosa*. Many MDR Enterobacteriaceae will be susceptible to tigecycline, and it can be considered a treatment option in those cases. In vitro data suggest that most *A. baumannii* strains can be inhibited with clinically achievable concentrations of

tigecycline, although resistance has been described. It should be noted that tigecycline does not have an FDA-approved indication for the treatment of *A. baumannii* infections [17].

6 Role of the Primary Care Provider in Managing Gram-Negative Infections

Primary care providers are in a unique position to improve the use of antimicrobial agents in the community and, subsequently, to help avoid unnecessary antimicrobial resistance in all settings. Indiscriminate use of antimicrobials has serious consequences, many of which have had, and will continue to have, a direct effect on patient care. For Example, a large study found that approximately 70% of patients seen in outpatient clinics for chief complaint of "sore throat" received a prescription for antibiotics [18]. Given that *Streptococcus pyogenes* is the only major bacterial cause of pharyngitis, that it causes approximately 20% of cases (with most being viral), and that a rapid diagnostic test is available, far fewer patients should receive antimicrobial therapy. In addition, 70% of patients who received an antibiotic received a non-recommended agent (mostly fluoroquinolones and macrolides). While streptococcal pharyngitis is obviously not a gram-negative infection, indiscriminate use of fluoroquinolones and macrolides, among other agents, certainly has an untoward effect on gram-negative pathogens such as *E. coli, K. pneumonia*, *H. influenzae,* and others. In certain geographical areas, empiric fluoroquinolone therapy for STD is no longer recommended due to resistance. The proper use of antimicrobials for any given disease requires knowledge of the likely pathogens, likely resistance issues, and proper diagnosis. Microbiologic studies should be used whenever possible to tailor therapy. Proper culture and susceptibility techniques can allow the clinician to narrow therapy if appropriate or to alter initial therapy if resistance is detected. The correct antimicrobial regimen for any infection is the one that eradicates the pathogen and has as little effect as possible on non-pathogenic commensal organisms.

7 Lack of New Agents in the Development Pipeline

While several new agents have recently been marketed for gram-positive infections, the outlook for the treatment of MDR gram-negative organisms is considerably bleaker. Mostly due to the huge costs, many pharmaceutical companies are shying away from the development of novel antimicrobial agents. Even those that have been recently marketed, such as tigecycline, have limitations in their activity. In the case of tigecycline, that limitation is the lack of efficacy *P. aeruginosa*. In 2006, the Infectious Diseases Society of America (IDSA) advocated a legislative

response to this public health crisis [2]. Until such actions come to fruition, clinicians have a responsibility to practice antimicrobial restraint when possible. The reader is referred to the IDSA's guidelines on Antimicrobial Stewardship for a more in-depth review of this topic [19].

Key Points

- Resistance in gram-negative pathogens is increasing and may be due to a variety of mechanisms.
- Beta-lactamase production, especially those of the broad-spectrum variety, presents unique challenges and should provide the impetus for the development of compounds that escape this resistance mechanism.
- Detection of extended-spectrum beta-lactamases (ESBLs) in clinical microbiology laboratories is technically difficult and may be subject to reporting error.
- Carbapenems are typically viewed as the drugs of choice for ESBL-producing gram-negative pathogens.
- Empiric therapy for serious infections should be broad spectrum and take into account local resistance patterns. The likelihood of a successful outcome is increased dramatically if empiric therapy is appropriate and initiated promptly.
- Few novel antimicrobial agents for MDR gram-negative pathogens are in the development pipeline. Antimicrobial stewardship should help preserve the current armamentarium.

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Tuberculosis

Vidya Sundareshan and Martin E. Evans

1 Epidemiology

In 2007, it was estimated that 2.2 billion persons, or one-third of the world's population, was infected with *Mycobacterium tuberculosis* [1] and the organism caused 1.6 million deaths. A decade after identifying TB as a global emergency, it still remains the second leading infectious cause of death among adults [2]. The mortality rate has steadily declined since it peaked at 400 deaths/100,000 persons in 1750, when the disease occurred in association with migration to cities during the Industrial Revolution. When streptomycin was introduced in 1946, the mortality rate was 33/100,000. By 2005, the mortality in the United States had declined to <1/100,000 [3]. Global mortality rates, however, currently average 24/100,000, with the highest rates in India (29/100,000) [1]. The AIDS epidemic is responsible for the rise of TB cases in many parts of the world, and co-infection with both HIV and TB contributes significantly to TB-related mortality.

Today, the expected cure rate for disease caused by drug-susceptible *M. tuberculosis* approaches 100% [4], but the emergence of antibiotic resistance has complicated the management of TB and increased the chance of treatment failure. The cure rate for infections caused by bacteria resistant to isoniazid (INH) or rifampin (RIF) (termed multidrug-resistant tuberculosis, or MDR-TB) is only 80–95%. The prognosis of MDR-TB is even worse in patients co-infected with HIV, with mortality rates up to 66% during treatment [5]. An emerging threat is from extensively resistant tuberculosis (XDR-TB), defined as resistance to INH, RIF, any fluoroquinolone, and at least one second-line injectable drug (amikacin, kanamycin, or capreomycin) [6]. XDR-TB renders some patients practically untreatable with currently available drugs. In one series from KwaZulu-Natal, South Africa, the mortality rate was 98% among patients infected with XDR-TB.

M.E. Evans (✉)
Lexington Veterans Affairs Medical Center and University of Kentucky School of Medicine, Lexington, KY, USA
e-mail: martin.evans@uky.edu

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The median survival was 16 days from the time of the first sputum collection. In the United States, the mortality rate may be up to 12% in patients with XDR-TB [7].

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. During 2005 in the United States, the overall prevalence of primary resistance to INH was 7.3% (4.1% among US-born persons and 9.8% among foreign-born persons) and the overall prevalence of acquired resistance to INH was 14.6% (9.1% in US-born persons and 19.7% in foreign-born persons). In the same year, the overall prevalence of primary MDR-TB in the United States was 1% (0.4% in US-born and 1.4% in foreign-born persons). MDR-TB in previously treated cases was 4.7% (1.3% in US-born and 7.9% in foreign-born persons) [3]. The prevalence of XDR-TB in the United States in 2006 was approximately 0.02% (17 cases). More than 80% had no prior history of TB and therefore could be considered to have primary XDR–TB [7].

Worldwide, from 2002 to 2007, the median prevalence of primary resistance to INH was estimated to be 10.3% (ranging from 0% in certain countries in western Europe to 42.4% in Tashkent, Uzbekistan), and the median prevalence of acquired resistance to INH was 27.7% (ranging from 0 to 81.2% in Tashkent, Uzbekistan) [8]. The worldwide prevalence of MDR-TB among all TB cases in 2006 was estimated to be 5.3%. The prevalence of primary MDR-TB was 2.9% and the prevalence of acquired MDR-TB was 15.3%, with the highest in Tashkent, Uzbekistan (60%) [8]. The overall global prevalence of XDR-TB in 2006 was estimated to be 2% [9]. XDR data available from developed countries indicate it ranges from 0 up to 33.3% (in Ireland and Slovenia). Data on primary and acquired XDR-TB are not available from all countries, but approximately half of the 53 XDR-TB cases reported from Kwazulu-Natal in South Africa had never received prior TB treatment.

2 Drug Resistance

Drug resistance in *M. tuberculosis* is caused by spontaneous mutations in the chromosome. Mutations associated with RIF and fluoroquinolone resistance occur at a frequency of approximately 10^{-8}, and mutations leading to INH, streptomycin, ethambutol (EMB), kanamycin, or *p*-aminosalicylic acid (PAS) resistance occur at a frequency of approximately 10^{-6}. Mutations leading to resistance to ethionamide, capreomycin, cycloserine, or thiacetazone occur at a frequency of approximately 10^{-3} [10].

These resistance frequencies are important because resistance to a combination of antibiotics, such as RIF plus 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 often contain 10^9 organisms [11], patients with cavitary TB may carry up to 1,000 organisms with primary resistance to INH and 10 organisms with primary resistance to RIF before receiving therapy. Because few, if any, bacteria are usually

resistant to both drugs, however, the probability of cure using both drugs is high since INH would kill RIF-resistant bacteria and RIF would kill 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 RIF would, in effect, be single-drug therapy with RIF alone. RIF resistance would develop among the INH-resistant population at a frequency of 10^{-8}. The patient might improve initially while RIF kills the majority of the bacteria, but then strains resistant to both drugs would emerge, and the patient would relapse.

Clinicians' prescribing behavior can lead to drug resistance. In 1977, Byrd and co-workers assessed the management of TB by non-pulmonary physicians and concluded that 73% of the patients had been treated inappropriately [12]. 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) [13]. In a survey of tuberculosis management practices in Kentucky in 1999, investigators found that TB was diagnosed by culture in only 66% of patients (thus, no susceptibility data were obtained in the remaining patients); 12 different regimens were used to treat the patients; monitoring of bacteriologic cure was appropriate in less than 65% of cases; and DOT was used in only 38% of patients [14]. Reports from other locales have documented similar problems.

3 Treatment of Drug-Susceptible TB Disease

3.1 General

The treatment of TB is important for the patient and for the community. Any private provider undertaking the responsibility of treating a patient with TB must assume a public health function not only to prescribe an appropriate regimen but also to manage drug side effects and ensure adherence until treatment is completed. For this reason, it is often best for the practitioner to partner with the local health department to provide care for the patient. Local health departments can often provide medications, laboratory, and radiology support to the patient without charge and can provide outreach personnel who can visit the home and ensure directly observed therapy. The local health department often has resources to help maximize adherence to therapy including social service support; treatment incentives and enablers; housing assistance; referral for treatment of substance abuse; and coordination of tuberculosis services with those of other providers.

Several regimens have been recommended for the treatment of drug-susceptible pulmonary TB (Table 1) using first-line agents (Tables 2 and 3) [15]. Each regimen

Table 1 Drug regimens for culture-positive pulmonary TB caused by a drug-susceptible organism [15]

Initial phase			Continuation phase			
Regimen	Drugs	Interval and doses[‡] (minimal duration)	Regimen	Drugs	Interval and doses[‡,§] (minimal duration)	Range of total doses (minimal duration)
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)[¶]	1a	INH/RIF	7 days a week for 126 doses (18 weeks)[¶] or 5 days/week for 90 doses (18 weeks)	182–130 (26 weeks)
			1b	INH/RIF	Twice weekly for 36 doses (18 weeks)[#]	92–76 (26 weeks)
			1c**	INH/RPT	Once weekly for 18 doses (18 weeks)	74–58 (26 weeks)
2	INH RIF PZA EMB	7 days/week for 14 doses (2 weeks), then thrice weekly for 12 doses (6 weeks) or 5 days/week for 10 doses (2 weeks)[¶], then thrice weekly for 12 doses (6 weeks)	2a	INH/RIF	Twice weekly for 36 doses (18 weeks)[#]	62–58 (26 weeks)
			2b**	INH/RPT	Once weekly for 18 doses (18 weeks)	44–10 (26 weeks)

(continued)

Table 1 (continued)

Initial phase			Continuation phase			
Regimen	Drugs	Interval and doses[‡] (minimal duration)	Regimen	Drugs	Interval and doses[‡,§] (minimal duration)	Range of total doses (minimal duration)
3	INH RIF PZA EMB	Three times a week for 24 doses (8 weeks)	3a	INH/RIF	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)
4	INH RIF EMB	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)[¶]	4a	INH/RIF	7 days a week for 217 doses (31 weeks) or 5 days/week for 155 doses (31 weeks)[¶]	273–195 (39 weeks)
			4b	INH/RIF	Twice weekly for 62 doses (31 weeks)	118–102 (39 weeks)

Definition of abbreviations: EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

[‡] When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

[§] Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive 7-month (31 weeks, either 217 doses {daily} or 62 doses {thrice weekly}) continuation phase.

[¶] Five-day-a-week administration is always given by DOT.

[#] Not recommended for HIV-infected patients with CD4 cell counts <100 cells/μl.

** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have positive culture from the specimen obtained at 2 months of being on this regimen, treatment should be extended an extra 3 months.

Table 2 Dosage recommendations for the initial treatment of drug-susceptible TB among children and adults [15]

Drugs	Daily		Dosage 2 times/week		3 times/week	
	Children	Adults	Children	Adults	Children	Adults
Isoniazid	10–15 mg/kg Max 300 mg	5 mg/kg Max 300 mg	20–30 mg/kg Max 900 mg	15 mg/kg Max 900 mg	Not recommended Not recommended	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	Not recommended Not recommended	10 mg/kg Max 600 mg
Pyrazinamide*	15–30 mg/kg Max 2 g	15–25 mg/kg Max 2 g				
Ethambutol*	15–20 mg/kg Max 1 g	15–20 mg/kg Max 1.6 g				

*See [15] for intermittent dosing based on body weight.

Table 3 Drugs used for tuberculosis [15]

Antimicrobial	Usual dose	Major side effects (1–10%)
First-line drugs		
Isoniazid	300 mg orally daily	Gastrointestinal, hepatitis, peripheral neuropathy
Rifampin	600 mg orally daily	Gastrointestinal, discoloration of urine, tears, etc., drug interactions
Rifabutin	300 mg orally daily	Same as rifampin
Rifapentine	600 mg orally each week	Same as rifampin
Pyrazinamide	15–25 mg/kg/day	Malaise, gastrointestinal, arthralgia, myalgia
Ethambutol	15–20 mg/kg/day	Optic neuritis, peripheral neuropathy, nausea/vomiting
Second-line drugs		
Levofloxacin	500–1,000 mg/day	Headache, gastrointestinal, rash
Gatifloxacin	400 mg/day	Headache, gastrointestinal, rash
Moxifloxacin	400 mg/day	Headache, gastrointestinal, rash
Streptomycin	15 mg/kg/day intramuscularly	Deafness, vertigo, renal dysfunction
Amikacin	15 mg/kg/day intravenously or intramuscularly	Deafness, vertigo, renal dysfunction
Kanamycin	15 mg/kg/day intravenously or intramuscularly	Deafness, vertigo, renal dysfunction
Capreomycin	15 mg/kg/day intravenously or intramuscularly	Deafness, vertigo, renal dysfunction
Cycloserine	500 mg orally each morning, 250 mg orally each evening	Central nervous system, congestive heart failure, rash, hepatitis, tremor
p-Aminosalicylate (PAS) (Paser® granules)	4 g packet mixed in orange juice or apple juice twice daily	Gastrointestinal upset
Ethionamide	250 mg orally each morning, 500 mg orally each evening	Central nervous system, Stevens–Johnson, gastrointestinal, SLE syndrome

has an initial phase of 2 months, followed by a choice of several options for a continuation phase of 4 or 7 months. In all regimens INH, RIF, pyrazinamide (PZA), and EMB are begun initially. INH and RIF are the most active agents. Relapse rates are 0–4% with INH- and RIF-susceptible *M. tuberculosis*; 2–7% with INH-resistant bacteria; and up to 72% if the bacteria are RIF resistant [16]. The inclusion of PZA is essential for the rapid sterilization of cavities, but the ability of PZA to prevent the emergence of resistance is low. For this reason, the fourth drug, EMB, is recommended initially. EMB can be stopped as soon as the laboratory confirms that the isolate is susceptible to INH and RIF. PZA should be continued for 2 months, at which time the use of the other agents and the duration of therapy should be

assessed based on the presence of cavitary lung disease on the initial chest radiograph and/or persistently positive smears and cultures for acid-fast bacilli (Fig. 1). Probably the simplest continuation phase includes rifapentine (Priftin^{TM}, Hoechst Marion Roussel Kansas City, MO). This drug has a half-life of over 13 h, which allows it to be administered once each week along with INH in HIV seronegative patients.

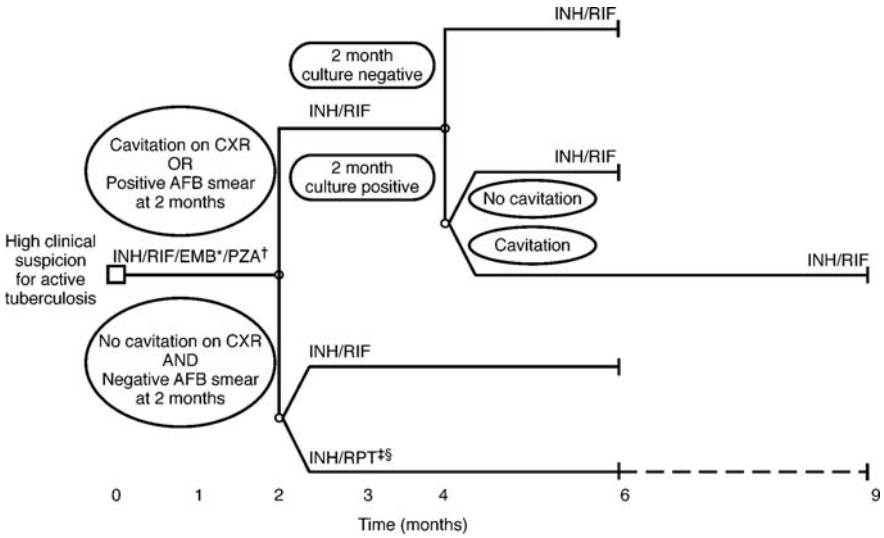

Fig. 1 Treatment algorithm for tuberculosis. Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at the completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the CD4 cell count is <100/μl, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifapentine, or daily or thrice-weekly isoniazid and rifampin, to complete a total of 6 months (*bottom*). Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months) [15]

*EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.

†PZA may be discontinued after it has been taken for 2 months (56 doses).

‡RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.

§Therapy should be extended to 9 months if 2-month culture is positive.

CXR, chest radiograph; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

The resolution of cough, fever, and weight loss are important clinical signs of success. The patient's sputum should be cultured on a monthly basis until two consecutive negative sputum cultures have been documented. Conversion should occur within 4 months if the regimen is successfully going to treat the patient's disease [15].

Clinicians should be aware of, and know how to manage, side effects of anti-tuberculous drugs. Ideally, all TB drugs are given at one time to increase compliance with DOT, but this may initially cause gastrointestinal symptoms for the first few weeks of therapy. Ingestion of the drugs with food may moderately decrease the absorption of anti-tuberculosis drugs but may ameliorate gastrointestinal symptoms.

INH can cause a peripheral neuropathy, although this side effect is rare (less than 0.2%). Pyridoxine (vitamin B_6) at a dose of 50 mg per day should be given with INH in persons with conditions that predispose them to neuropathy, such as diabetes; alcoholism; nutritional deficiency; HIV infection; renal failure; pregnancy; and breastfeeding, to prevent this side effect. Color vision and acuity must be assessed periodically if the patient is taking EMB, which can cause optic neuritis.

It is important to monitor the serum aspartate aminotransferase (AST) level monthly for patients on potentially hepatotoxic drugs such as RIF, INH, and PZA. All TB therapy should be held if AST levels are more than three times the upper limit of normal in the presence of symptoms (anorexia, nausea, vomiting, right upper quadrant pain, jaundice) or more than five times the upper limit of normal in the absence of symptoms. The patient may be left without TB therapy for a short time while AST levels normalize, or alternative agents can be prescribed after consultation with an expert. Once AST levels decrease to less than two times the upper limit of normal and symptoms significantly improve, the medications can be restarted in sequential fashion with a new drug added every 2–3 days (EMB, then PZA, then RMP, then INH) with careful monitoring of symptoms and AST levels.

Healthcare providers should also be aware of drug–drug interactions, which are especially common with the rifamycins.

3.2 Directly Observed Therapy (DOT) and Combination Antimicrobial Preparations

Patient non-compliance with prescribed therapy for TB 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. In 1993, the Advisory Council for the Elimination of Tuberculosis of the Centers for Disease Control and Prevention (CDC) recommended that DOT be considered for all patients in areas that do not achieve a 90% completion rate of therapy. The World Health Organization currently recommends DOTS (directly observed treatment – short course) for all TB patients worldwide [15]. DOT is designed to help the patient take all doses of medications

and prevent the emergence of resistance. In DOT, a healthcare 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 is more likely to remain sensitive to the initial antibiotic regimen.

DOT has been successful in improving compliance and decreasing TB case rates. Control of an 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 utilize intermittent therapies with twice- or thrice-weekly dosing regimens if possible.

The use of fixed-dose combinations of anti-tuberculous drugs also has been proposed as one method to improve compliance and prevent drug resistance [17]. Rifamate™ (Hoechst Marion Roussel), containing 150 mg INH and 300 mg RIF per tablet, and Rifater™ (Hoechst Marion Roussel), containing 50 mg INH, 120 mg RIF, and 300 mg PZA per tablet, are currently the only two fixed-dose combination products on the US 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 under-dosed. This might allow the emergence of resistance to all agents simultaneously.

When difficulties arise with anti-tuberculous 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.

3.3 Considerations for Patients Co-infected with HIV

The immunosuppression due to human immunodeficiency virus (HIV) infection impairs the host response to infection with TB, and TB accelerates the progression of HIV disease. It is estimated that 13 million persons are co-infected with HIV and TB worldwide. Concurrent HIV infection is estimated to confer more than a 100-fold increased risk for development of active TB compared to HIV-negative persons. Those with advanced HIV infection are at most risk of developing active TB infection.

Treatment of TB in HIV-infected persons can be very complex for a number of reasons. First, drug resistance may be more common in HIV-infected patients

than in uninfected persons. In one report, resistance rates among HIV-infected and non-infected patients were 11.3 and 5.5% for INH; 8.9 and 1.6% for RIF; 5.1 and 1.8% for PZA; and 6.2 and 1.3% for combined INH and RIF (MDR), respectively [18]. 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 the resulting drug metabolism. Protease inhibitors, for instance, inhibit the CYP450 system and decrease the metabolism of other drugs. Among the non-nucleoside 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 RIF > rifapentine > rifabutin. Dosing in other drugs used in combination with the rifamycins often must be adjusted. Guidelines published by the CDC (http://www.cdc.gov/tb/) should be reviewed for specific drug–drug interactions. For these reasons, it is strongly recommended that patients with TB–HIV co-infection be managed by providers experienced in the management of both diseases.

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" or immune reconstitution inflammatory syndrome (IRIS) and is thought to be due to restoration of the immune system by antiretroviral therapy. The incidence of these reactions ranges from 7 to 36%. It usually begins within 15 days of starting antiretroviral therapy, is associated with decreases in viral load, and may last from 1 to 7 months [15].

4 Treatment of Drug-Resistant TB Disease

Drug resistance should be suspected in a patient (1) who has had prior therapy; (2) from an area where drug resistance is prevalent; (3) when sputum smears remain positive after 2 months of therapy; (4) when sputum cultures remain positive after 4 months of therapy; and (5) when there is unexplained worsening of the patient's chest radiograph or clinical course. Furthermore, a drug should be considered of dubious efficacy if testing reveals that it was the only drug in a prescribed regimen to which the bacterium is sensitive and the drug had been used for more than 1 month.

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

When INH, RIF, PZA, or EMB cannot be used because of drug resistance, second-line agents must be employed. In general, these agents (Table 3) are less desirable than first-line agents because they are more toxic and there is less clinical experience with their efficacy. For this reason, it is important to seek consultation with an expert when dealing with drug-resistant TB.

Among second-line agents, cycloserine is usually well tolerated, but can have substantial central nervous system toxicity. This may be manifested as impaired mentation, psychoses, suicidal ideation, or seizures. The addition of pyridoxine (50–100 mg/day) may be of some benefit. PAS is usually well tolerated when given in the form of Paser^{TM} granules (Jacobus Pharmaceutical Co., Inc., Princeton, NJ). In this formulation, the drug is adsorbed to methylcellulose beads. Patients may be concerned about the appearance of methylcellulose beads in their stools. The drug is not well absorbed unless it is given in an acid medium such as orange juice, cranberry juice, or applesauce. Ethionamide is the most poorly tolerated antibiotic, especially if it is given with PAS. Gastrointestinal side effects including nausea, vomiting, diarrhea, and a metallic taste are commonly reported. The injectable drugs streptomycin, amikacin, and kanamycin are valuable adjuncts to any re-treatment regimen. Their principle toxicities affect the kidney, vestibular, and auditory systems. Serum creatinine and drug levels should be monitored carefully as well as monthly audiometry and clinical examinations of vestibular function.

Recommended regimens for treatment of resistant TB should be based on bacterial susceptibility testing and are listed in Table 4. The following principles should be observed in designing a re-treatment regimen in addition to those recommended for the treatment of drug-susceptible TB (see below):

Table 4 Potential regimens for management of patients with drug-resistant tuberculosis [15]

Pattern of drug resistance	Suggested treatment	Duration of treatment
INH (±SM)	RIF, PZA, EMB (FQ may strengthen regimen for extensive diseases)	6
INH and RIF (±SM)	FQ, PZA, EMB, IA ± alternative agent	18–24
INH, RIF (±SM), and EMB or PZA	FQ (EMB or PZA if active), IA and two alternative agents	24
RIF	INH, EMB, FQ supplemented with PZA for the first 2 months (an IA may be included for patients with extensive disease in the first 2–3 months)	12–18

Definitions of abbreviations: EMB, ethambutol; IA, injectable agent; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; SM, streptomycin; FQ, fluoroquinolone; most experience involves ofloxacin, levofloxacin, or ciprofloxacin, injectable agents may include aminoglycosides (streptomycin, amikacin, kanamycin) or the polypeptide capreomycin; alternative agents= ethionamide, cycloserine, *p*-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid.

1. Never add a single drug to a failing regimen.
2. Re-treatment should not be begun until reliable susceptibility data are available from the laboratory.
3. Consider prior treatments. Regard with suspicion any drug that has been used for more than 1 month in a regimen where it was the only active agent. Such a drug may have diminished activity regardless of in vitro susceptibility testing data.
4. A re-treatment regimen should contain at least three drugs, including an injectable one. Regimens employing four to six agents provide better results in patients with MDR organisms in whom there is resistance to first-line agents in addition to INH and RIF.
5. Consider the relative in vitro efficacy of antibiotics against *M. tuberculosis*. Among second-line drugs, ethionamide > amikacin > kanamycin = capreomycin > cycloserine=PAS. Among the fluoroquinolones, levofloxacin > gatifloxacin=moxifloxacin.
6. There is no point in continuing drugs that have failed clinically and/or to which the organism is resistant in vitro.
7. Therapy should always be initiated in the hospital. This allows for monitoring of compliance and side effects.
8. DOT is essential in treatment of drug-resistant TB. Do not use intermittent regimens for drug-resistant TB.
9. Consider monitoring serum drug peak and trough levels since the pharmacokinetics of second-line anti-tuberculous drugs is often unpredictable. This is especially true in AIDS patients.

The success of therapy should be gauged as it is with drug-susceptible tuberculosis. Patients should improve clinically and cultures should become negative. Thereafter smear and culture should be obtained every 2 months for the next 2 years. Parenteral agents are usually continued for 6 months and oral drugs for a total of 18–24 months after the sputum culture becomes negative. 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.

Traditional indications for surgery in TB have been massive hemoptysis, bronchopleural fistulae, bronchial stenosis, or trapped lung. Recently the addition of surgery to the management of MDR-TB has been recommended, but there are no randomized studies to support definitely its benefit [15]. If surgery is to be done, it should be postponed, if possible, until the patient has had at least 3 months of medical therapy in an attempt to clear the sputum of mycobacteria. Long-term antibiotic therapy is still required after surgery to achieve high cure rates [19]. Chances of positive outcome with surgery are much higher in patients with localized disease, good nutritional status, good medical treatment after surgery, and the availability of an experienced surgeon [20].

5 Preventive Regimens for TB Disease (Treatment of Latent TB Infection)

Persons exposed, but without active TB disease, represent a reservoir of infection. The lifetime risk for progression from latent TB infection (LTBI) to active TB is approximately 5% in the first year of infection, and 5% for the remainder of the lifetime of an individual not infected with HIV. In HIV-infected individuals, the risk of progression to active disease approaches 10% per year [21]. Nursing home residents are also at increased risk of reactivation due to immunodeficiency related to aging, malnutrition, co-morbid illnesses, and use of immunosuppressive medications. In the past, persons previously infected with *M. tuberculosis* were thought to be relatively immune to re-infection. It is now known that re-infection can occur, especially if the patient has AIDS [21]. 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 [21].

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; recent immigrants from countries with high rates of TB infection; homeless persons; healthcare workers; residents or employees of long-term care facilities; and other persons with medical conditions which make them more susceptible to developing active disease. These include persons with diabetes mellitus; chronic renal failure; leukemia or lymphoma; carcinomas of the head, neck, and lung; jejunoileal bypass; gastrectomy; silicosis; or diseases resulting in $\geq$10% weight loss [21]. Also at risk are patients treated with anti-TNF-α antibodies (infliximab (Remicade®) or adalumimab (Humira®)) or the soluble TNF receptor, eternacept (Enbrel®). The necessity for preventive therapy is based on risk group and skin test reactivity (Table 5).

An alternative to the tuberculin skin test is a commercially available whole blood assay for interferon-γ (INF-γ) (QuantiFERON®-TB Gold, Cellistis, Inc., Valencia, CA). This ELISA test measures INF-γ elaborated from memory T cells of individuals previously exposed to *M. tuberculosis*. The test appears to have increased specificity for diagnosis of LTBI (86–99%) compared to the tuberculin skin test, but like the skin test, it cannot be used to distinguish active TB infection from LTBI. The CDC suggests that the QuantiFERON®-TB Gold test may be used in any circumstance in which the tuberculin skin test is currently used [22].

In most cases, INH is the drug of choice for the treatment of LTBI [21]. Generally, the drug is given at a dose of 300 mg daily or 900 mg of INH twice weekly for 9 months. Alternative regimens include 4 months of RIF (600 mg/day), and a 2-month regimen of RIF (600 mg/day) and PZA (20 mg/kg/day). The latter is generally not recommended any longer because of unacceptable hepatotoxicity [23].

Table 5 Candidates for preventive therapy [21]

Tuberculin skin test with ≥ 5 mm induration
• HIV-infected persons, or persons with high-risk behaviors
• Recent contacts of a person newly diagnosed with infectious tuberculosis
• Persons with chest radiographs showing fibrotic lesions likely to represent old TB
• Persons with organ transplants or other immunosuppressive medical conditions (receiving the equivalent of prednisone ≥15 mg/day for 1 month or more)
Tuberculin skin test with ≥ 10 mm induration
• Recent immigrants (within past 5 years) from high-prevalence countries
• Injection drug users
• Residents and employees of high-risk congregate settings (e.g., prisons, jails, nursing homes, homeless shelters)
• Mycobacteriology laboratory personnel
• Persons with clinical conditions that place them at high risk (see text above)
• Children <4 years of age, or infants, children, or adolescents exposed to adults at high risk
Tuberculin skin test with ≥ 15 mm induration
• Persons with no risk factors for TB

Regimens for the preventive therapy of presumed resistant TB are not well established. INH is probably of little value for persons exposed to INH-resistant TB. The 4-month RIF regimen (see above) may be appropriate in this setting. For preventive therapy of persons exposed to MDR-TB, the 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 [21]. Persons in these categories should receive preventive therapy with at least two drugs. A combination of PZA (25–30 mg/kg/day) and EMB (15–25 mg/kg/day), or PZA and levofloxacin (500–1,000 mg daily) has been recommended [21]. The antibiotics should be given for 12 months. 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, patients should be followed clinically and treated if they develop disease based on the susceptibility of the isolates recovered. The second is to treat with PZA and EMB or PZA and levofloxacin, as above.

Key Points

- If TB is suspected, always obtain sputum to get an isolate.
- Do antimicrobial susceptibility testing on the isolate to guide therapy.
- Begin empiric treatment with four drugs.
- Use directly observed therapy (DOT).

- Manage drug-susceptible TB in close coordination with the local health department.
- Manage HIV–TB co-infection and drug-resistant TB in consultation with an expert.

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Community-Acquired Viral Infections

Chris Parsons

1 Influenza Virus

1.1 Virology

Influenza is an RNA virus of the orthomyxovirus family. Influenza A viruses are classified into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). Genetic evolution resulting in alterations in H or N proteins accounts for the diversity and adaptability of these viruses. Antigenic shift refers to the emergence of influenza viruses encoding novel H or N antigens, possibly the result of genetic reassortment, although the precise origin of pandemic influenza strains is unknown. Antigenic shifts resulted in the global pandemics of 1918, 1957, 1968, and 1977. Antigenic drift refers to the emergence of influenza viruses encoding novel H or N antigens as the result of point mutations in the genes for H and/or N, and results in less extensive and severe influenza outbreaks than antigenic shift. Antigenic characteristics of circulating strains provide the basis for selecting the virus strains used in each year's influenza vaccine. Infection or vaccination targeting previous strains typically does not result in protective immunity to strains resulting from antigenic drift. Major epidemics of respiratory disease are caused by influenza virus strains not represented in that year's vaccine [1–3].

1.2 Epidemiology

Each year, approximately 10–20% of United States residents develop clinically significant infections caused by influenza. Previous pandemics caused the greatest morbidity and mortality among younger, more susceptible members of the

C. Parsons (✉)
Division of Infectious Diseases, Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: parsonch@musc.edu

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population. Recently, 80–90% of influenza-related deaths have occurred in individuals greater than 65 years of age, especially when influenza A type H3N2 has predominated. Between 1972 and 1992, influenza infections claimed the lives of approximately 21,000 individuals annually. It is the fifth leading cause of death in individuals over 65, and the most common infectious cause of death in the United States. Rates of disease are increased in individuals 65 years of age or older and in those with underlying health problems, including cardiovascular disease, diabetes, and renal disease. These high-risk groups are more likely to require hospitalization due to secondary complications such as bacterial pneumonia, worsening of chronic respiratory or cardiac disease, and primary influenza pneumonia [1, 2, 4].

1.3 Clinical Syndromes

Influenza is transmitted from person to person by virus-laden aerosolized particles released by infected persons during coughing, sneezing, and talking. The abrupt onset (1–2 days) of fever, myalgia, sore throat, and a nonproductive cough characterize influenza infection. Unlike other common respiratory illnesses, infection with influenza may cause easy fatiguability lasting for several days. The symptoms vary based on age, as children commonly present with cough, rhinorrhea, and croup, while adults present with cough, myalgia, sore throat, and headache. Despite the relatively common presence of severe sore throat, oropharyngeal findings on physical examination are unusual. Cervical adenopathy may be present, especially in younger patients. The elderly most commonly complain of cough alone, or in combination with headache [1–3].

Complications of influenza infection include primary influenza pneumonia, secondary bacterial pneumonia, and myositis. Primary influenza pneumonia occurs when influenza virus infection directly involves the lung, typically producing a more severe respiratory syndrome. Clinical suspicion for primary influenza pneumonia should be raised when symptoms persist and increase instead of resolving in a patient with acute influenza. High fever, dyspnea, and even progression to cyanosis can be seen. Exacerbation of fever and respiratory symptoms after initial improvement in the symptoms of acute influenza may signify the onset of secondary bacterial pneumonia, an important complication of influenza infection. This is most often caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Haemophilus influenzae* [5]. Myositis and rhabdomyolysis have been reported most frequently during influenza infections in children. Although myalgias are a prominent feature of most cases of influenza, true myositis is uncommon. The hallmark of myositis is extreme tenderness of the affected muscles, most commonly in the legs. In the most severe cases, swelling and bogginess of the muscles may be noted. Markedly elevated serum creatine phosphokinase (CK) concentrations are seen, and myoglobinuria with associated renal failure has been reported [6, 7].

1.4 Diagnosis

During the initial evaluation of patients with symptoms suggestive of influenza, several other infectious agents must be considered in the differential diagnosis including RSV, parainfluenza virus, adenoviruses, enteroviruses, *Mycoplasma* and *Chlamydia* species, and *Streptococcus pyogenes*. Diagnostic testing for influenza should be considered when patients exhibit suggestive signs and symptoms during the appropriate season of the year. Although viral culture is the gold standard for laboratory diagnosis, it takes 48–72 h to confirm cytopathic effects of the virus in tissue culture [8]. Rapid viral diagnostic tests employing immunological and molecular techniques are becoming increasingly available. The sensitivity and specificity of rapid influenza-antigen tests have been compared to the reference standard of viral culture and range from 72 to 95% (sensitivity) from 76 to 84% (specificity) [9]. Another factor that influences sensitivity is the timing of the test in relationship to clinical symptoms. Viral shedding peaks at 24–48 h of illness and then rapidly declines, and viral replication is rarely detectable in the respiratory tract after 5–10 days [10]. PCR-based testing is more sensitive than culture and should be used if possible in place of the rapid antigen test.

1.5 Prevention

Resolution of influenza infection typically occurs within 5–7 days. Supportive therapies include bed rest, oral hydration, and acetaminophen to reduce fever. Immunoprophylaxis with inactivated (formalin-killed) vaccine is recommended for certain high-risk groups, and antiviral agents may shorten the disease course and decrease secondary complications [11].

Vaccine: The influenza vaccine contains three virus strains that are predicted to circulate in the United States during the upcoming influenza season. The vaccine usually contains two influenza A strains and one influenza B strain made from highly purified, inactivated, egg-grown viruses. Following vaccination, the patient develops antibodies to hemagglutinin. Maximal antibody titers occur within 2–4 weeks and decline within 10 months. The elderly and those with underlying chronic medical conditions may have diminished antibody responses and remain susceptible to influenza infections, although vaccination can still prevent lower respiratory-tract involvement or other secondary complications in this setting. 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].

Influenza vaccination is recommended for (1) persons aged 50 years and older; (2) residents of nursing homes or chronic care facilities; (3) individuals who

Effectiveness of influenza vaccination

Population	% Illness prevented	% Hospitalizations and pneumonia prevented	% Death prevented
Healthy <65	70–90		
65 years and older not in a chronic care facility		30–70	
65 years and older in a chronic care facility	30–40	50–60	80

References [1].

have underlying medical conditions, including pulmonary, cardiovascular, renal, hepatic or metabolic disorders (including diabetes), asplenia, immune suppression, or neurologic conditions that may compromise respiratory secretions; (4) individuals 6 months to 18 years of age who receive long-term aspirin therapy and have an increased risk for developing Reyes syndrome after being infected with influenza virus; (5) women who will be pregnant during the influenza season; and (6) employees of hospitals, outpatient settings, nursing homes, and other chronic care facilities that care for high-risk patients [12]. Travelers who have not previously been vaccinated during the appropriate season may also benefit from vaccination.

Although side effects may be noted in a small minority of recipients following vaccination, the vaccine does not cause influenza-related illness. Known side effects of the vaccine include

1. Soreness at the injection site.
2. Systemic symptoms: Fever, malaise, and myalgia are more common in those that have never been exposed to the antigens in the vaccine (typically children). The reaction usually begins 6–12 h after the vaccination and lasts for 1–2 days.
3. Hypersensitivity 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–Barre Syndrome (GBS): One to two cases of GBS occur per 1 million doses of the influenza vaccine. It is unclear whether the vaccine itself causes GBS, although patients diagnosed with GBS appear to be at no increased risk for complications from the vaccine [13, 14]. It may be prudent to withhold vaccination from patients who develop GBS within 6 weeks of receiving the influenza vaccine.

Due to the decline of antibody titers and the antigenic variation observed year to year, individuals should receive the vaccine annually. 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 since antibody levels may decline within a few months of vaccination.

Influenza vaccine dosing recommendations are as follows:

Age group	Vaccine	Dose	Number of doses[a]	Route
6–35 months	Split virus only	0.25 cc	1 or 2	Intramuscular
3–8 years	Split virus only	0.50 cc	1 or 2	Intramuscular
9–12 years	Split virus only	0.50 cc	1	Intramuscular
> 12 years	Split or whole virus	0.50 cc	1	Intramuscular

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

An intranasal, live-attenuated, cold-adapted, trivalent vaccine may represent an effective and convenient approach in children. Efficacy in individuals 1–5 years of age ranged from 86 to 100% [15, 16].

Chemoprophylaxis: Oseltamivir and zanamivir, two inhibitors of the viral neuraminidase, are currently the only drugs recommended for the prevention of influenza in the United States. This recommendation is based upon the efficacy of these drugs and the lower rates of resistance compared to the adamantanes. In a meta-analysis of seven prevention trials, prophylactic therapy with oseltamivir or zanamivir was associated with a relative reduction in the odds of developing influenza of 70–90%, depending upon the population studied and the strategy adopted [17]. The recommended prophylactic dose of oseltamivir is 75 mg once daily. The recommended prophylactic dose of zanamivir is 10 mg (two inhalations) once daily. The usual duration of therapy varies with the indication. Prophylactic antiviral therapy should begin within 2 days after exposure to an infected individual and should be given for 7–10 days [18]. During community outbreaks, prophylaxis in unvaccinated individuals may be given throughout the period of peak influenza activity or throughout the entire influenza season (usually 6–8 weeks). The development of immunity following vaccination takes about 2 weeks; as a result, prophylactic therapy should be considered for the following persons:

1. High-risk persons during an outbreak of influenza A: These individuals should still be vaccinated, but the development of protective antibodies can take up to 2 weeks. If these individuals have significant risk of secondary complications, chemoprophylaxis should be considered. Antiviral therapy does not interfere with antibody response to the vaccine. If the patient is a child receiving the vaccine for the first time, extended chemoprophylaxis should be considered (i.e., continue for 2 weeks after the second vaccine injection).

2. Individuals who have close contact with patients diagnosed with influenza. This includes family members or healthcare workers previously unvaccinated who come in close contact with patients with influenza.
3. Immune deficiency: Individuals who are expected to have an inadequate antibody response and are at high-risk for secondary complications should be offered 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.

1.6 Treatment

Neuraminidase inhibitors: 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 when therapy is initiated within 48 h of the signs and symptoms of infection. Treatment benefits include a decrease in the time to clinical resolution by 1–1.5 days. 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, where the drug may cause bronchospasm and/or decline in lung function. No studies have compared zanamivir with the adamantanes, amantadine or rimantadine. Zanamivir is dosed 10 mg (two oral inhalations at 5 mg/inhalation) every 12 h, for 5 days. 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 [19–21].

The prodrug oseltamivir (GS4104), the first FDA-approved oral neuraminidase inhibitor, has been approved for the treatment of influenza types A and B. Dosed at 75 mg, twice a day for 5 days, oseltamivir indications include adults with acute uncomplicated illness and those who present within 48 h of symptom onset. When given to individuals between the ages of 18 and 65, a 1- to 2-day decrease in time to clinical improvement was observed compared to the placebo group, and the drug reduced both illness severity and the incidence of secondary complications of influenza. Major adverse events included nausea and vomiting in less 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 when the drug is taken with food [1, 22, 23].

Adamantanes: Multiple studies have also shown that treatment with amantadine or rimantadine is effective in reducing the severity and duration of symptoms related to influenza A, if given within 48 h of illness. Drug-resistant virus can emerge after treatment of children or adults and then transmitted to family contacts.

Amantadine and rimantadine dosing recommendations:

Population	Type of TX	Amantadine	Rimantadine
Child ≤45 kg or age 1–9 years old	Treatment	5 mg/kg/day up to 150 mg in 2 divided doses	Not approved for treatment
	Prophylaxis	5 mg/kg/day up to 150 mg in 2 divided doses	5 mg/kg/day up to 150 mg in 2 divided doses
Age 10–13 years old	Treatment	100 mg bid	Not approved for treatment
	Prophylaxis	100 mg bid	100 mg bid
Age 14–64 years old	Treatment	100 mg bid	100 mg bid
	Prophylaxis	100 mg bid	100 mg bid
Age 65 years old	Treatment	≤ 100 mg/day	100 or 200 mg/day
	Prophylaxis	≤ 100 mg/day	100 or 200 mg/day

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 day one then 100 mg/qd	≥10	No change
	15–29	200 mg on day one then 100 mg/qod	≤10	100 mg/day
	≤15	200 mg every 7 days		
Liver dysfunction	No change	100 mg/day in severe cases		
Seizure	Close observation	Close observation		

References [1, 2].

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

The following are the side effects when young healthy adults are dosed with 200 mg/day:

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 in patients with renal insufficiency and the elderly on 200 mg/day dosing, 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].

1.7 Antiviral Resistance

Compared to the adamantanes, neuraminidase inhibitors have been less likely to promote the onset of viral resistance, with rates of resistance in influenza A viruses approximating 1–5% in clinical trials and less in ambulatory care settings prior to 2007 [24]. The Centers for Disease Control and Prevention reports an 8% rate of resistance of H1N1 influenza viruses to oseltamivir in the United States in the 2007–2008 season [25]. The H1N1 mutation responsible for the oseltamivir resistance described above causes >400-fold reduced susceptibility of H1N1 influenza virus to oseltamivir, but does not cause resistance to zanamivir [26].

2 Herpes Simplex Viruses

2.1 Virology

Herpes simplex viruses (HSV) are enveloped double-stranded DNA viruses. 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. HSV establishes latent infection following entry into sensory nerve endings during 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, including 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 [27, 28].

Greater 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 five 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 years 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 approximately 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 approximately 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 the city (compared to suburbs) have a higher prevalence of HSV II. The seroprevalence is approximately 10% from ages 15 to 29 and 35% by age 60 with a three to fourfold higher rate in African-Americans, relative 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 directly correlates with acquisition of infection (Table 1) [27, 28].

Table 1 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

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 approximately 2% per gestation, with transmission to the fetus related to the shedding of the virus at the time of 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 [27].

2.2 Clinical Syndromes

2.2.1 Mucocutaneous Infection

Following exposure of mucosal surfaces or abraded skin to HSV I, vesicular lesions on an erythematous base appear after an incubation period of 2–12 days (mean of 4 days) [27, 28]. HSV may be shed from oral lesions for up to 23 days (mean of 7–10 days) and the duration of symptoms may last 2–3 weeks. Asymptomatic infection is the most common outcome of HSV exposure. Fevers of 101–104F occur with symptomatic infection. In primary gingivostomatitis, but rarely during recurrent infection, submandibular lymphadenopathy can occur. Other common symptoms include sore throat, malaise, and tender cervical lymphadenopathy. Children are more likely to present with painful buccal and gingival involvement and an inability to tolerate liquids. The elderly often present with pharyngitis and mononucleosis-like

symptoms. During the initial evaluation, the physician must consider herpangina (usually due to coxsackieviruses), candida infections, Epstein–Barr virus, Stevens–Johnson syndrome (especially if the patient is on medications), and lesions induced by chemotherapy or radiation therapy.

Recurrent infections are usually preceded by a prodrome of pain, burning, tingling, or itching approximately 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. Vesicles last 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 days and the lesions heal in approximately 3 weeks. 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 primary HSV II infection are attenuated 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. Primary infection can result in a urinary retention syndrome in 10–15% of the cases, and aseptic meningitis in up to 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 females, 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 days with viral shedding lasting 2–5 days. Neurologic and systemic complications are uncommon in recurrent disease, but paresthesia and dysesthesias may occur. The frequency of recurrences varies 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 to three. Transmission of the virus may 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 occurring in patients with underlying atopic dermatitis, and herpes gladitorium. Both HSV I and II can trigger erythema multiforme.

2.2.2 Neonatal Disease

The incidence of neonatal HSV infection ranges from one case per 2,000–5,000 deliveries per year, resulting in 1,500–2,200 cases annually in the United States

[27–29]. The transmission from mother to fetus is influenced by several factors. During primary maternal infection, the transmission rate is 30–50%, compared with 3% during recurrent infection. The presence of maternal antibodies may reduce the severity and the likelihood of transmission. Rupture of membranes for more than 6 h can result in ascending infection of the neonate via the cervix. Inoculation of newborns may also occur following inoculation at the site of fetal scalp monitors.

About 75–80% of infections are acquired through intrapartum contact with infected genital secretions of the mother. The remainder of vertical 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. Due to the high mortality, these neonates should be diagnosed and treated within the first 24 h. Other neonatal HSV infections include: those localized to the skin, eye, and mouth; encephalitis with or without skin involvement; and disseminated infection involving CNS, lungs, liver, adrenal glands, skin, eye, and/or mouth. Relatives and hospital personnel with orolabial herpes may also spread HSV to newborns.

2.2.3 Keratoconjunctivitis

HSV is the most common cause of corneal opacification and infection-related vision loss in the industrialized world. HSV I is the major agent beyond the neonatal period [27, 28, 30, 31]. The incidence of new and recurrent episodes is 20.7 per 100,000 person-years. Primary infection is often asymptomatic and results in 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 with similar frequency to that of 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. Active disease with the initial episode of keratitis averages 2–3 weeks, while recurrent episodes last approximately 1 month. In 90% of cases, visual acuity of 20/40 or better will be maintained [17, 20, 21].

2.2.4 HIV and HSV

Genital herpes with HSV II has been linked to both the acquisition and transmission of HIV-1 and represents the most frequent sexually transmitted disease among HIV-1 seropositive individuals [27]. Since 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 infection 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 as well as chronic, persistent mucocutaneous disease. HSV infection in this setting can

present as large ulcerative lesions involving any area of the body, although 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 infection, including mucocutaneous ulcers lasting $\geq$1 month, bronchitis, pneumonitis, or esophagitis are more likely to occur in those with CD4 counts $\leq$100 cells/mm^3 and may be the first clinical manifestation of HIV infection.

2.2.5 CNS Infections

HSV accounts for 10–20% of all cases of viral encephalitis and is the most common cause of fatal sporadic encephalitis in the United States [27, 32]. The incidence of this disease is three per 100,000 cases and, beyond the neonatal period, is typically caused by HSV I. HSV II may cause aseptic meningitis in adults, and these patients present without the mental status changes seen with encephalitis. Treated appropriately, HSV encephalitis still incurs a mortality of approximately 30%, while mortality in untreated patients exceeds 70%, with <3% of survivors regaining normal neurologic function. Patients typically present within 7 days of symptom onset. About 90% of these patients present with fever and focal neurologic findings, including 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.

2.2.6 HSV in Pregnancy

Approximately 1,500–2,200 cases of neonatal herpes occur each year in the United States, most often due to HSV II. Due to 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 infection during pregnancy, which can lead to an increased risk of preterm labor, intrauterine growth retardation, and spontaneous abortion. These infections occur during any phase of pregnancy. Those patients with the highest risk of acquiring the infection are young, single women with a history of previous sexually transmitted diseases. Vertical transmission and pregnancy-related morbidity for women infected early in their pregnancy is uncommon [33]. Acquisition of the disease near the time of delivery, however, results in vertical transmission and complications [33]. Table 2 reflects the rates of maternal–fetal transmission of HSV based on maternal infection [28, 29, 33].

2.3 Treatment

No cure for HSV exists, but steps can be taken to prevent transmission, and antiviral therapies reduce viral shedding and healing time. The main issue concerning genital HSV transmission, however, is preventative care. Individuals exhibiting high-risk

Table 2 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

behaviors and those with current infection, even if asymptomatic, should be educated on the proper use of condoms and behavioral modification to decrease the risk of spreading and acquiring HSV.

Acyclovir is a synthetic acyclic purine nucleoside analog, and its derivatives with greater oral bioavailability include the prodrug valacyclovir (converted to acyclovir) and famciclovir (converted to penciclovir). 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. Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome has been associated with high-dose valacyclovir therapy in HIV-infected and transplant patients, although a cause–effect relationship is unproven.

For mucocutaneous infections, therapy shortens the duration of viral shedding and length of time to healing while reducing associated pain, if initiated within 24 h of onset. These effects are more demonstrable for primary HSV infection. Even with early initiation of therapy, the frequency of recurrences is not affected. Treatment of asymptomatic individuals will also reduce shedding and HSV transmission to uninfected partners, although this effect is lost with discontinuation of the medication. Table 3 describes the therapeutic options for HSV infections.

Suppressive therapy should be considered in individuals with more than six episodes per year, or in those with severe cases as with HIV infection. Therapy can be initiated in adherent patients at the start of symptom prodrome to decrease the length of time to healing. The FDA has approved therapy for 12 months with acyclovir, although studies have demonstrated efficacy with no cumulative toxicity over 5 years. Patients on suppressive therapy should have dose adjustments or trials of discontinuation of suppressive therapy every 12 months to assess the need for continued therapy. It may be safe to discontinue suppressive therapy in HIV-infected patients once their CD4 count rises above 350 cells/mm^3.

2.4 Pregnancy

Since the greatest risk of vertical transmission occurs near the time of delivery, patients should be educated on abstinence and the use of condoms during the third trimester – especially if the HSV status of the partner is unknown. The FDA

Table 3 Treatment of genital HSV infections

Infection	Acyclovir	Valacyclovir	Famciclovir
Initial episode	200 mg PO 5×/day × 5–10 days 5 mg/kg iv q8h × 5 days 5% ointment topically q6h × 7 days		
Recurrent episode	200 mg PO 5×/day × 5 days 400 mg PO tid × 5 days 800 mg PO bid × 5 days	1,000 mg PO bid × 5–10 days	250 mg PO tid × 5–10 days
Suppression	200 mg PO tid	500 mg PO bid × 5 days	125 mg PO bid × 5 days
Immuno compromised	400 mg PO bid	250 mg PO bid 500 mg PO qd	250 mg PO bid
Initial episode	200–400 mg PO 5×/day × 10 days 5 mg/kg iv q8h × 7–10 days (or up to 14 days in HIV-infected patients)		
Recurrent episode	200–400 mg PO 5×/day × 5–10 days	500 mg PO bid × 10–14 days	125–250 mg PO bid × 10–14 days
Suppression	200 mg PO tid 400 mg PO bid	500 mg PO bid × 5–10 days	125–250 mg PO bid × 10–14 days
HSV encephalitis	10 mg/kg iv q8h × 10–14 days	500 mg PO qd 500 mg PO bid	125–250 mg PO bid
Neonatal HSV	10 mg/kg iv q8h × 10–14 days	*	*
HSV in pregnancy	See special cases below	*	*
HSV resistance	See special cases below		

*Signifies that these drugs are not used in these clinical settings.
References [27, 32, 34, 35].

has categorized current antiviral medications as class C (acyclovir) and class B (valacyclovir and famciclovir) for use in pregnancy. 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. Guidelines on the treatment of pregnant women remain controversial among experts in the field [33, 36, 41].

For treatment of a primary infection in the first and second trimester, standard doses for genital infections should be employed. Suppressive therapy over the last 4 weeks 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 in the third trimester, Cesarean section should be considered in all patients, especially if symptoms occur within 4 weeks 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 that are considered high risk for vertical transmission, procedures that could damage the newborn's skin and create a portal of entry for infection (e.g., scalp electrodes, fetal blood sampling, and instrumental delivery) should be minimized.

For treatment of a recurrent infection, normal vaginal delivery is indicated 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 on an individual basis. The available evidence suggests that the risks of vaginal delivery for the fetus are small and must be weighed against the risks to the mother of a Cesarean section.

2.5 Resistance in Immunocompromised Patients

The prevalence of acyclovir-resistant HSV infection in immunocompromised patients with HIV infection or stem-cell transplantation is approximately 5%. Viral resistance is promoted by the degree of immunosuppression of the patient and by prolonged use of acyclovir, although resistance emerging during chronic suppressive therapy is relatively uncommon. Cross-resistance for valacyclovir and famciclovir would be expected in this setting, as the mechanisms of resistance are similar for these agents [42]. If the patient has not responded to initial therapy within 14 days, 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/hr until the lesions have crusted have been demonstrated.

If these regimens fail, antiviral-susceptibility testing may be indicated and consideration given for therapy with foscarnet or cidofovir. 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 and complete re-epithelialization has occurred (usually after 2–3 weeks). Cidofovir is currently approved for the treatment of cytomegalovirus disease and should only be considered in individuals who have failed high-dose acyclovir and foscarnet. The major adverse event is renal tubular toxicity. In order to diminish this nephrotoxicity, both hydration and probenecid dosed pre- and post-infusion are recommended. Cidofovir is dosed at 3–5 mg/kg intravenously weekly for 2–4 weeks. Once lesions have resolved, recurrent infections are typically caused

by acyclovir-susceptible HSV; therefore, therapy with acyclovir or related agents should be initiated as first-line therapy in this setting [35, 43, 44].

3 Varicella Zoster Virus

Like the HSV, *Varicella-zoster* virus (VZV) is an enveloped, double-stranded, DNA virus. 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.

3.1 Epidemiology

VZV is spread person-to-person by direct contact or aerosolization from skin lesions or respiratory-tract secretions, and the mucosa of the upper respiratory tract and conjunctiva are the main portals of entry. VZV is transmissible to susceptible hosts from the source individual from approximately 2 days prior to symptom onset until skin lesions begin to crust over. Of the four million cases of varicella per year, 33% occur in preschool children (1–4 years of age) and 44% occur in school age children (5–9 years 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 due to the greater intensity of exposure. Only 5% of varicella infections are subclinical (i.e., without rash).

A history of VZV infection is a reliable marker for immunity with a positive history 97–99% predictive of serologic immunity. Approximately 70–90% of individuals with a negative history of VZV are also seropositive.

Preventative measures are important for the control of nosocomial transmission of VZV. After exposure to VZV, susceptible employees can serve as vectors with transmission to patients. VZV has been reported in hospital employees without direct contact with patients having active lesions but exposed to air from the patient's room [45].

Herpes zoster is more common in adults and the immunocompromised, 75% of cases occur in patients over the age of 45. Immunocompetent children, adolescents, and young adults may develop herpes zoster, although in adolescents and young adults, this should prompt concern for HIV infection in patients with risk factors for HIV. Acute acquisition of VZV is not associated with herpes zoster.

3.2 Clinical Syndromes

3.2.1 Varicella

Varicella in children is a self-limited disease of 4–5 days duration and incurs fever, malaise and a generalized, pruritic, vesicular rash that starts on the face and scalp then spreads to the trunk and extremities. The incubation period is 10–21

days. Successive crops of vesicular lesions appear over 2–4 days and eventually become purulent and crust over. Thus, the simultaneous presence of different stages of vesicular lesions is characteristic of varicella. Complications from varicella include infection with beta-hemolytic Group A streptococci, pneumonia, meningoencephalitis, cerebellar ataxia, and hepatitis. Reyes syndrome associated with aspirin use during VZV infection is now considered uncommon [46]. Adolescents and adults are at greater risk for complications, particularly varicella pneumonia, and exhibit a higher mortality rate.

Although perinatal infection is uncommon given maternal immunity to VZV, intrauterine VZV infection may result in fetal varicella syndrome (low birth weight, cutaneous scarring, limb hypoplasia, microencephaly, cortical atrophy, chorioretinitis) if maternal infection occurs during the first half of the pregnancy. The incidence of fetal varicella syndrome with VZV infection in weeks 1–12 is 0.4% and weeks 13–20 is 2%. Varicella infection of the mother 5 days before to 2 days 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 [47, 48].

3.2.2 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, although it is most often limited to a single dermatome in immunocompetent patients. The characteristic rash consists of closely cropped small vesicles, often referred to as "dew drops on a rose petal." Vesicles typically crust over within 10 days and completely heal within 1 month. The most common complication of herpes zoster is pain, referred to as postherpetic neuralgia. Postherpetic neuralgia most often affects those over 50 years of age and can be severe, lasting for weeks to months. Pain may also precede the appearance of the rash [49].

Although less common, VZV infection, with or without the typical rash, may cause more severe clinical manifestations. CNS syndromes caused by VZV include meningitis, radiculitis, meningoencephalitis, and stroke syndromes. When the trigeminal nerve is involved, especially the ophthalmic branch (zoster ophthalmicus), complications include dendritic keratitis, anterior uveitis, iridocyclitis, and panophthalmitis. Zoster oticus (involvement of the vestibular nerve) may result in hearing compromise and brain-stem involvement. One form of this disease, Ramsey Hunt Syndrome, is characterized by vesicles located in the auditory canal with coincident facial nerve paralysis [50, 51].

In the immunocompromised host (HIV-infected or organ transplant recipient), reactivation of VZV may result in a disseminated infection with a generalized eruption along with central nervous system, pulmonary, hepatic, and pancreatic involvement. Disseminated zoster in these hosts, and thus the need for more diligent evaluation and monitoring, is signified by involvement of more than one dermatome.

3.3 Diagnosis

The clinical features of acute varicella infection in children, and the unilateral, dermatomal rash seen in herpes zoster, are sufficiently characteristic of these illnesses that diagnostic testing is usually not necessary. However, herpes simplex, measles, and other causes of vesicular eruptions may mimic herpes zoster. Although viral culture is the traditional gold standard for identifying VZV from vesicle fluid, more recently developed PCR assays are more sensitive. In addition, PCR and intrathecal serologic tests can be useful in diagnosing CNS VZV infections [50, 51].

3.4 Antiviral Therapy

Acyclovir, when given within 24 h of onset of varicella, decreases the number of lesions and the formation of new lesions, the 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. However, children at risk for complications of varicella should receive acyclovir, including those with cutaneous or cardiopulmonary disorders, and those on chronic corticosteroids [52]. Since varicella is a more severe disease in adolescents, adults, and immunocompromised children, treatment with acyclovir is recommended [53, 54]. 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 [55]. Treatment must begin early because in the immunocompetent host, viral replication is undetectable 72 h after the rash appears.

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 those over the age of 50 who have a greater incidence of postherpetic neuralgia [56]. While steroids do not reduce the incidence of postherpetic neuralgia, the addition of prednisone to acyclovir during acute primary herpes zoster decreases the duration of pain and the return to daily activities [57].

Valacyclovir, a prodrug of acyclovir with better absorption and higher serum levels, is also approved for the treatment of herpes zoster [58]. Famciclovir, a prodrug of penciclovir, is effective in treating varicella and herpes zoster [59]. The advantage of valacyclovir and famciclovir is convenience: both are dosed 3 times a day instead of 5 times per day with acyclovir. Famciclovir and valacyclovir may decrease the duration of postherpetic neuralgia but not its incidence in elderly patients.

Since therapeutic levels after oral administration are unreliable, intravenous acyclovir is recommended for severe VZV infections in the setting of disseminated disease, transplant recipients, and HIV-infected patients. Adequate hydration

must be maintained during intravenous acyclovir administration to prevent ACV precipitation in the renal tubules resulting in acute renal failure.

In summary, acyclovir is recommended for high-risk children and adults with varicella. Valacyclovir or famciclovir are recommended in the initial treatment of zoster, given their superior pharmacokinetic profiles.

Disease	Valacyclovir	Famciclovir	Acyclovir
Varicella Immunocompetent Host			20 mg/kg (maximum 800 mg) 4 times daily for 5 days
Varicella Immunocompromised Host			10 mg/kg intravenously every 8 h for 7–10 days
Herpes Zoster Immunocompetent Hosts	1 g 3 times daily for 7 days	500 mg 3 times daily for 7 days	800 mg 5 times daily for 7 days
Herpes Zoster Immuno compromised Host			10 mg/kg intravenously every 8 h for 7 days
Herpes Zoster Immuno compromised Host Acyclovir-resistant virus	Foscarnet 40 mg/kg intravenously 3 times daily for 7–14 days		

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.

3.5 Prevention

3.5.1 Post-exposure Prophylaxis

Varicella Zoster Immune Globulin (VZIG)

If given to exposed persons, particularly immunocompromised children, within 96 h of exposure to someone with varicella, VZIG may prevent or ameliorate varicella infection. Protection lasts for 3 weeks with a single dose of VZIG. Unfortunately, VZIG is nearly depleted due to the discontinuation of its production by the manufacturer [60].

VariZIG

VariZIG is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies. This product is lyophilized

and must be reconstituted for intramuscular injection. VariZIG is currently recommended for immunosuppressed patients and pregnant women with documented exposure to persons with varicella, who lack either a history of VZV vaccination or detectable VZV IgG antibodies. VariZIG should be administered with 96 h of exposure. An expanded access program is available through the manufacturer (800-843-7477) [61].

IVIG

If VZIG or VariZIG cannot be administered, IVIG (400 mg/kg 1-time dose) should be considered, although no data currently exist for its utility in this setting.

3.5.2 Vaccination

A live, attenuated VZV vaccine has been developed and proven effective in preventing both varicella and herpes zoster. 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. The vaccine is also effective in preventing or modifying varicella infection if given within 3 days of exposure to persons with varicella. Herpes zoster and the severity of illness, including the duration of pain, are also reduced in vaccinees [60].

The Advisory Committee on Immunization (ACIP) has recommended that all children entering child care facilities and elementary schools receive the VZV vaccine if they lack evidence of varicella immunity (physician diagnosis of varicella, reliable history, or serologic evidence) [60]. The first dose is recommended at age 12–15 months, with a second vaccine recommended for 4–6 years of age. Since the risk of severe varicella is high in adolescents and adults, the vaccine is also recommended for persons over 13 years of age lacking evidence of prior immunity. Two doses should be given 4–8 weeks apart in this age group.

The 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 $\geq$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, and it is clear that vaccinated persons >5 years removed from vaccination are at greater risk for acquiring VZV and for suffering more severe disease [62]. Therefore, it is unclear whether vaccinees with no history of VZV exposure will require additional booster vaccinations to prevent severe varicella infections later in life, although vaccination every 5 years may eventually be warranted.

4 Respiratory Syncytial Virus

4.1 Virology and Epidemiology

RSV is a single-stranded RNA virus and member of the Paramyxoviridae family. Subtypes A and B are often both present in outbreaks, although subtype A is associated with more severe disease. 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, RSV infections generally begin in November, peak from January to March, then continue through April to mid-May. Approximately 120,000 children are hospitalized and 4,500 deaths occur annually in the United States due to the complications of RSV.

About 50–69% of all children develop primary RSV infection by the age of 12 months with 15–22% having lower respiratory involvement. One-half to 2% will be hospitalized with a mortality of 0.5–3.5%. By 2 years of age, greater than 95% have been infected with RSV. Immunity following infection is short-lived, and re-infection occurs throughout life. Re-infection rates in preschool aged children range from 40 to 70%, with approximately 20% recurrences in school-aged children, adolescents, and adults.

RSV is highly infectious and easily transmitted from person to person by close contact. The primary modes of transmission include direct contact with large secretion droplets (small particle aerosol is not a significant mode of transmission) and self-inoculation of the eyes and nose with 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 sources include rubber gloves (90 min), gowns (30 min), and hands (25 min). Good hand washing and proper disposal practices are, therefore, important since infected individuals shed the virus for 1–21 days (mean of 6.7 days), even if asymptomatic [63, 64].

Increased disease severity is associated with low socioeconomic status, ethnicity, male gender, young age, body mass of less than 5 kg, prematurity, chronic lung disease, congenital heart disease (especially in association with pulmonary hypertension), and T-cell immunodeficiency. Increased risk of acquiring the disease occurs in crowded conditions (two or more individuals sharing a bedroom), school age siblings, multiple births, lack of breast feeding, passive smoke exposure, day-care attendance, and birth within 6 months prior to an anticipated RSV season [63, 65].

4.2 Disease Pathogenesis

The average incubation period of RSV is 5 days. Symptoms can range from cold-like symptoms to severe bronchiolitis or pneumonia. Symptomatic re-infection typically presents with milder illness. The hallmark of infection – involvement of the small intrapulmonary airways – results in the classic clinical syndrome of bronchiolitis.

Lower respiratory-tract infections are due to transfer of the virus from the upper respiratory tract and results 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, immunity to RSV is transient and imperfect. Recurrent upper respiratory infections are probably due to the transient nature of immunity of IgA. In contrast, lower respiratory-tract resistance appears to be more durable [63, 65].

4.3 Neonatal Infection

Newborns typically acquire RSV via contact with visitors and health care personnel. The clinical variation and rare clinical occurrence of lower respiratory-tract involvement in individuals less than 3 weeks of age is probably due to the presence of maternally derived neutralizing antibodies. Signs of upper respiratory tract infections occur in less than 50% of infected neonates and are highly variable and nonspecific. These clinical signs include poor feeding, lethargy, and irritability.

4.4 Infection in Infants

Infants younger than 1 year who have low RSV antibody titers and are not breastfed have an increased risk of developing lower respiratory tract disease in the first 5 months of life. One of the early manifestations in this age group following RSV infection is apnea. This occurs more readily in infants less than 6 weeks of age, those who are born prematurely, and those with low arterial oxygenation saturations. Mechanical ventilation, if required, is necessary for approximately 48 h, with postextubation apnea being uncommon.

Infants with severe disease and in need of more intensive monitoring can be identified with six independent clinical and laboratory findings: (1) oxygen saturation of less than 95%, determined by pulse oximetry; (2) atelectasis on chest radiograph; this occurs in 50% of hospitalized patients and may be the only radiographic finding in 15% of the cases; diffuse interstitial pneumonitis, hyperexpansion, and subsegmental consolidation, typically in the right upper or middle lobe (25% of cases), also occur; (3) respiratory rate greater than or equal to 70 breaths per min; (4) gestational age less than 34 weeks; (5) age less than 3 months; and (6) “Ill” or “toxic” appearance. If hospitalization is required, the length of stay is typically 4–7 days, with full recovery at about 2 weeks. 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 hyper-reactivity or pulmonary function abnormalities by the ages of 8–12.

4.5 Childhood Infection

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 to 40°C during the first 2–4 days of the illness, nasal discharge, pharyngitis, and cough. Hoarseness and laryngitis are uncommon. By the time these children present to their local health care facility, lower respiratory tract symptoms are more prominent. Signs and symptoms are based on the severity of disease and can include increased cough, increased respiratory rate of up to 80 breaths per min with substernal and intercostal retractions during inspiration, a prolonged expiratory phase, hypoxemia typically without cyanosis, hyperexpanded and hyperresonance in the chest, and intermittent rales and wheezes.

4.6 Infection in Adults and the Elderly

Infection with RSV after the age of 2 most commonly manifests as an upper respiratory tract illness or tracheobronchitis. Typically, symptoms include nasal congestion and cough with a more severe and prolonged course as compared to "colds" caused by other respiratory viruses. 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 present with mild nasal congestion, but fever, anorexia, pneumonia, or bronchitis may develop [66, 68].

4.7 Diagnosis

A diagnosis of RSV pulmonary syndrome should be suspected during the appropriate winter season when involving children under 1 year of age, the elderly, or immunocompromised adults, and if bronchiolitis is present. The standard test for diagnosing RSV is viral growth in culture, using nasal wash or nasopharyngeal swab samples for inoculation. Rapid antigen testing and PCR methodologies are largely supplanting culture for diagnosis given their more rapid turnaround time and increased sensitivity in some settings [69–71].

4.8 Treatment

The mainstays of therapy consist of respiratory support, nutrition, and hydration. Bronchodilators (beta-agonists and epinephrine) and anti-inflammatory agents

(cromolyn sodium and budesonide) have demonstrated some clinical utility, but further studies are required to confirm these findings [63, 65]. The use of antivirals in the treatment of RSV infections also remains controversial.

Ribavirin is the only antiviral agent licensed for the treatment of RSV infections. Ribavirin is dosed at 6 g/300 cc of water over 18 h or 6 g/100 cc of water over 2 h, 3 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 [72]. Cohort studies also failed to demonstrate an improved clinical outcome with ribavirin therapy [73, 74]. 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 [75]; however, most clinicians do not use aerosolized ribavirin because of the limited clinical benefit, cost, and difficulty in administration. In addition, ribavirin should not be used for pregnant women, given its teratogenicity in animal models.

4.9 Prevention

Palivizumab is an FDA-approved humanized monoclonal antibody directed against an RSV surface glycoprotein. Initial studies of palivizumab dosed at 15 mg/kg IM every month for 5 months during the peak RSV season demonstrated an overall reduction in RSV-related hospitalizations by 55%, with significant reductions in infection of 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%) [76, 77]. 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, thus, has no risk of transmitting blood-borne pathogens. Given more recent data for the use of palivizumab in high-risk pediatric patients, it is recommended for the following groups: children under 2 with bronchopulmonary dysplasia, children under 2 who have hemodynamically significant congenital heart disease, and children under 1 born <28 weeks gestation, or under 6 months born 29–32 weeks gestation with risk factors for RSV acquisition [77–79].

Interrupting transmission at health care 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. The table below lists 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 hand washing Procedures following any contact with RSV-infected patients or fomites, even if gloves are used.
- Limit visitors. Do not allow visitors 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.

Ref. [64, 69].

Key Points

- Illnesses caused by influenza, HSV, VZV, and RSV are commonly seen in outpatient settings and incur substantial morbidity and mortality.
- Prevention is important to control these viral illnesses. Influenza and varicella are effectively managed through vaccination. HSV transmission can be prevented through behavioral changes, education, and occasionally medical treatment. In high-risk individuals, RSV infection can be reduced by immunoprophylaxis.
- Antiviral agents are used effectively to decrease morbidity and mortality for these illnesses. Although resistance to older antiviral agents has been seen, the advent of newer therapies for these infections has reduced concern for the effect of resistance on the outcomes of these infections.

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Influenza

Christian Sandrock

1 Introduction

Influenza is a dynamic, widespread virus that causes disease in a broad range of hosts with far-reaching public health effects. The influenza virus belongs to the genera *Orthomyxoviridae* and causes an acute respiratory tract illness in children and adults. Influenza undergoes frequent and extensive genetic changes, allowing for a yearly seasonal pattern of recurrent infections along with the development of novel subtypes that have the potential to create larger pandemics. More recently, avian subtypes have begun to cause disease in humans who have had direct contact with infected birds. Unfortunately, resistance to antiviral agents has emerged over the last few years. Influenza is one of the most influential viruses in history, and will undoubtedly continue to affect public health and challenge clinicians and policymakers in the future.

2 Basic Virology

2.1 Viral Structure

Influenza A, *B*, and *C* are the most important genera of the *Orthomyxoviridae* family. *Influenza A* is responsible for human pandemic outbreaks and seasonal epidemics, and *Influenza B* is responsible for increasing numbers of cases of seasonal disease. *Influenza C* causes rare human disease, mostly in children. Influenza viruses are enveloped, single-stranded RNA viruses with a segmented genome. The eight RNA segments of the genome encode for 11 viral proteins, including the polymerase proteins (PB1, PB2), matrix proteins (M1, M2), and the surface glycoproteins hemagglutinin (HA) and neuroaminidase (NA) (Table 1). *Influenza A* viruses are classified into subtypes on the basis of the antigenic properties of the HA and NA

C. Sandrock (✉)
University of California Davis Health System, Sacramento, CA, USA
e-mail: cesandrock@ucdavis.edu

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glycoproteins expressed on the surface of the virion. To date, 16 HA and 9 NA subtypes have been identified and are found in 144 different combinations (e.g., H1N1, H3N2, H5N1) (Table 1) [1, 2].

Table 1 Characteristics of influenza viruses

	Influenza A	Influenza B	Influenza C
Genetic structure	8 segments	8 segments	7 segments
Viral proteins	10 total	11 total	9 total
Unique viral protein	M2	NB	HEF
Antigenic determinants	Hemagglutinin (HA) and neuroaminidase (NA)	HA and NA	HA and NA
Genetic change	Antigenic shift and drift	Antigenic drift	Antigenic drift
Host range	Avians, humans swine, marine mammals, horses	Humans	Humans and swine
Human epidemiology	Pandemics and seasonal epidemics	Seasonal epidemics	No seasonality

The HA glycoprotein mediates attachment and entry of the virus by binding to sialic acid receptors on the cell surface. The binding affinity of the HA to the host sialic acid allows for the host specificity of *Influenza A*. Once inside the cell, viral replication begins immediately with the cessation of host cell protein synthesis. The NA glycoprotein allows the spread of the virus by cleaving the glycosidic linkages to sialic acid on the host cells and the surface of the virus. The virus is then spread via bodily fluids or through direct contact with secretions. Viral synthesis and release occurs for approximately 12–24 h, and then eventual cell death occurs due to cessation of host protein synthesis and cell-mediated apoptosis driven by the influenza infection [2].

2.2 Genetic Changes

Influenza A viruses are highly variable, due to molecular changes in the RNA segments that occur through a number of mechanisms; the most important are point mutation (antigenic drift) and RNA segment reassortment (antigenic shift). Like other RNA viruses, the *Influenza A* viruses lack proofreading ability and are therefore subject to point mutations. These individual mutations in the viral genome cause minor changes in the antigenic character of the virus, with amino acid changes in HA and NA of principal importance. This drift occurs as the virus travels and replicates through a susceptible population. Subsequent disease caused by a new strain created from antigenic drift is less severe than with a novel strain, as partial immunity within the population often remains, but the extent of the seasonal epidemic varies yearly [2–4].

Reassortment occurs when a host cell is infected with two or more *Influenza A* viruses and leads to the creation of a novel subtype containing a new HA or NA that is immunologically distinct from that of the previous circulating strains. The

three major pandemics that have occurred in the last century (1918 H1N1, 1957 H2N2, and 1968 H3N2) have been associated with reassortment. As *Influenza A* is host-specific, a less specific host, or "mixing vessel," that is more susceptible to all subtypes is required. Pigs, which possess receptors for both the human and avian subtypes, are a traditional "mixing vessel," but any species, including humans and wildlife, can potentially play a similar role. In the 1957 (H2N2) and 1968 (H3N2) pandemics, a pig was implicated as the intermediate host for viral "mixing" of two strains. Recent infections of humans with avian subtypes of *Influenza A* (e.g., H5N1) have heightened concerns that humans can function as a "mixing vessel" after direct infection from birds [2–4].

2.3 Virulence Features

Severe clinical findings occur with certain subtypes, for example, the 1918 H1N1 and some avian subtypes. The virulence factors responsible for severe disease outbreaks are becoming better understood. First, the binding location may determine the extent of local inflammation and severity of disease. Human virus subtypes H1, H2, and H3 bind to α-2,6 linkages found in human upper respiratory epithelium. Humans also have a smaller number of α-2,3 linkages, mostly located in their lower respiratory tract and conjunctivae; these are the preferred binding sites of the avian subtypes. Thus, binding of an avian subtype is more likely to occur in the lower respiratory tract and thus presents as pneumonia rather than as upper respiratory symptoms (Table 2) [5]. Second, local and systemic cytokine release varies with subtypes. In a mouse model of an engineered 1918 H1N1, significantly higher levels of specific cytokines, most notably IL-2, IL-6, and TNF were found locally and systemically [1, 5]. Additionally, the NS1 protein, which antagonizes host cell interferon, appears to have had increased activity. These characteristics of the deadly 1918 virus have also been found with the most recent severe human infections with influenza caused by the avian subtype H5N1 [1]. Finally, influenza viral replication is usually limited largely to the respiratory tract, but in some subtypes (e.g., H5N1) viremia has been detected, adding to the burden of disease [5].

Table 2 Characteristics and pathogenicity of *Influenza A* viruses

Viral features	
HA subtypes	16
NA subtypes	9
Predominant human subtypes	H1, H2, H3
Avian subtypes	H1–H16
Highly pathogenic avian influenza (HPAI) subtypes	H5 and H7
Conversion to high pathogenicity	Basic amino acid insertion in HA
Avian sialic acid-galactose linkages	α-2,3 linkages
Human sialic acid-galactose linkages	α-2,6 linkages

H or HA, hemagglutinin; HPAI, highly pathogenic avian influenza; NA, neuraminidase.

2.4 Pathogenicity Characteristics of Avian Influenza Viruses

In avian subtypes of *Influenza A*, the viruses are also characterized by their pathogenicity. Highly pathogenic avian influenza (HPAI) is defined by the World Organization for Animal Health (OIE) as any influenza that causes severe disease or death in domestic poultry. HPAI viruses, with very few exceptions, are of the H5 or H7 subtype, but not all H5 and H7 subtypes are HPAI viruses. The potential pathogenicity of H5 and H7 subtypes can be evaluated by sequencing the HA gene, since pathogenicity is associated with the presence of multiple basic amino acids at the HA cleavage site (Table 2). A change from a low pathogenic H5 or H7 subtype to a highly pathogenic form may occur upon introduction into poultry and is thought to occur primarily as a result of insertion of basic amino acids in the HA cleavage site. Molecular studies have shown that the 1918 human pandemic H1N1 subtype originated as a low pathogenic avian virus. In contrast, current human cases of H5N1 worldwide are the result of a highly pathogenic avian influenza virus.

2.5 Host Immune Responses to Influenza Virus

Immunity to influenza occurs through a number of steps. Initially, a large cytokine response occurs, characterized predominantly by IL-2, IL-6, and interferon gamma production. This leads to extensive local inflammation with neutrophils and macrophages infiltrating the sub-epithelium of the respiratory tract. Particularly with avian subtypes, this leads to a hemophagocytic syndrome and severe diffuse alveolar damage, causing the clinical findings of severe pneumonia and respiratory failure. Within the alveolar macrophages and pneumocytes, MHC I upregulation leads to antigen presentation of the hemagglutinin and other subcapsular proteins. This eventually leads to natural killer cell destruction of infected cells and the development of neutralizing antibodies (largely against HA) by day 14 of infection. When compared to human subtypes H1 and H3, infection with avian subtype H5N1 appears to infect lower respiratory tract cells, inhibit NK cell function, deplete lymphocytes, inhibit MHC class I upregulation, and inhibit cell apoptosis [2].

3 Epidemiology

3.1 Seasonal Influenza

Influenza follows a seasonal pattern with outbreaks occurring yearly in the winter months. *Influenza A* viruses predominate, with a H3N2 subtype currently making up the majority of isolates. *Influenza B* viruses are isolated more frequently late in the season and are more likely to be found in children [2]. *Influenza B* viruses are the most commonly reported influenza type in Europe, while both *Influenza A* and *Influenza B* viruses predominate in Asia and the southern hemisphere. Outside of the

winter season, influenza occurs infrequently. In temperate tropical regions, influenza can occur at lower levels throughout the year. Furthermore, summertime outbreaks of influenza have occurred on cruise ships or in individuals returning from areas of increased activity [2, 4]. *Influenza A* outbreaks typically begin abruptly, they peak over a 2–3 week period, and they last for 2–3 months. The earliest indication of influenza activity is an increase in febrile respiratory illnesses, usually in children and then adults.

The factors that determine the extent and severity of outbreaks vary yearly. The susceptibility of the population, as determined by the prevalence of antibodies to circulating virus, clearly plays a major role. Additionally, the virulence of the seasonal strains differ each year, and thus their efficiency of transmission or their ability to cause symptomatic infection will vary as well.

Influenza B outbreaks are generally less extensive and are associated with less severe disease when compared to *Influenza A* outbreaks. *Influenza B* has been reported most frequently in schools, military camps, and chronic care facilities. As with *Influenza A*, population immunity and the intrinsic virulence of the virus will affect severity in a given season. *Influenza C* causes very sporadic disease, mainly in children, without seasonality [2, 4].

3.2 Avian Subtypes

Over the past two decades, the incidence of avian subtypes of *Influenza A* directly infecting humans has dramatically increased. Land use changes, cultural practices, and worldwide poultry outbreaks have contributed to this increase. Initially, sporadic cases of avian influenza in humans occurred in both the United States and United Kingdom with subtype H7N7 (Table 3). Only a few cases of self-limiting conjunctivitis were reported in patients in each country, at the time of a poultry outbreak. The patients had each had contact with a sick bird without the appropriate protective equipment. Then, in 1997, a large-scale HPAI H5N1 outbreak occurred among poultry in Hong Kong farms and markets, and direct human disease occurred, with 18 documented human cases and 6 fatalities. Two subsequent poultry outbreaks in Hong Kong in 1999 and 2003 with HPAI H5N1 occurred without human cases until 2003, when two members of a family in Hong Kong contracted HPAI H5N1. In December of 2003, HPAI H5N1 surfaced in poultry in Korea and China, and from 2003 to 2006 the poultry outbreak spread worldwide. Human cases of HPAI H5N1 followed the poultry outbreak, with over 300 cases and 170 deaths to date [1, 6].

Although HPAI H5N1 is the largest outbreak, other notable avian subtypes have caused human disease in recent years. In 2003 in the Netherlands, a large poultry outbreak of H7N7 subtype resulted in 89 cases of influenza disease among poultry workers and a veterinarian; there was one death (the veterinarian). Two cases of conjunctivitis caused by subtype H7N3, a low pathogenicity strain, occurred among poultry workers during a Canadian outbreak in 2004. Finally, in 1999 and again in 2003, *Influenza A* subtype H9N2 caused a mild, self-limiting respiratory infection

in children during a poultry outbreak. Clearly, HPAI H5N1 is the largest and most significant poultry and human avian influenza outbreak recorded, but other subtypes have caused significant diseases as well (Table 3) [6].

Table 3 Influenza subtypes associated with human infection and disease

Influenza subtype
Seasonal subtypes
H1N1
H2N2
H3N2
Avian subtypes
H5N1
H7N7
H7N3
H9N2

Human cases of avian influenza have been mostly acquired by direct transmission from infected birds to humans. In each of the outlined outbreaks, the humans have consumed undercooked or raw poultry products or they have had direct contact with infected poultry or contaminated fomites. All birds have been ill or dead, and transmission has only been documented from domesticated poultry or waterfowl. No transmission to humans from wild birds has been reported. Thus far, human-to-human transmission has occurred in a few cases and with poor efficiency. During the 1997 HPAI H5N1 Hong Kong outbreak, one household contact of an ill poultry worker became infected. Health-care worker studies at the time also showed a 3.7% seroprevalance rate for H5 antibodies among the workers caring for the ill during the outbreak (0.5% in controls). During the 2003 worldwide HPAI H5N1 outbreak, two family clusters were suspected, and in 2004 one case of daughter to mother transmission was confirmed in Thailand. An additional family cluster from Indonesia with eight infections from a single source was also suspected in 2007 [1]. Three subsequent studies of health-care workers in Thailand, Vietnam, and China all showed not nosocomial transmission. Finally, in 2003 during the H7N7 outbreak in the Netherlands, three cases of household contacts with minimal disease were reported [1, 6].

3.3 Pandemic and Novel Strains

Novel strains of influenza develop through reassortment or antigenic drift. If the novel strain has little immunity in the general population, if it causes disease, and it is transmittable from human to human, then the likelihood for a pandemic is high. The advent of a pandemic may initially be noted by severe cases, particularly in young, lower risk adults, and an elevated mortality. The number of cases may be exceedingly high and also may occur outside of the winter season. Additionally, the excess mortality related to influenza may be higher in the first or second season. For

example, in North America, the majority of influenza-related deaths in 1968/1969 and 1969/1970 occurred during the first pandemic season [2, 4].

4 Clinical Features

4.1 Seasonal Influenza in Adults

Infection by influenza begins by inhalation of virus-containing respiratory secretions from an infected person through small-particle aerosols or through direct contact with the virus. Respiratory secretions of infected persons that contain large amounts of virus are transmitted through sneezing, coughing, and talking. Viral spread and survival increases with lower temperatures and humidity. After initial infection, viral replication appears to occur only in the respiratory tract [7].

Influenza infections have a broad spectrum of presentation, ranging from afebrile respiratory illnesses similar to the common cold to illnesses with systemic signs and symptoms. After an incubation period of 1–2 days, influenza often begins with the abrupt onset of fever, headache, myalgias, and malaise. These symptoms are accompanied by respiratory tract illness with cough and sore throat. A few physical findings may be noted in uncomplicated influenza. Fever, flushing, and mild cervical lymphadenopathy may be present and are more frequent in younger patients. The respiratory examination is often normal, but on occasion, rales may be present. Uncomplicated influenza usually improves over 2–5 days, although the illness may last for 1 week or more. Some patients have persistent symptoms of weakness or easy fatigability, referred to as postinfluenza asthenia, which last for several weeks.

In certain individuals, particularly those at high risk, complications may occur [7]. Individuals at high risk for complications include those with renal disease, underlying pulmonary disease, and cardiovascular disease. Patients receiving immunosuppressive agents as well as those in chronic care facilities are also at risk. Pneumonia is the most common complication and can either be a primary or secondary pneumonia. Primary influenza pneumonia occurs when influenza directly infects the lower respiratory tract, with the disease usually being relatively severe. Those with cardiac and underlying pulmonary disease, such as obstructive lung disease, are the most susceptible to primary pneumonia. Secondary pneumonia, which is more common than primary pneumonia, occurs when bacteria invade and infect the lower respiratory tract after loss of the upper respiratory tract cilia's natural clearance mechanism. The most common complicating bacterial pathogens are *Pneumococcus*, *Haemophilis influenzae,* and *Staphylococcus aureus*. Over the past few years, methicilin-resistant *Staphylococcus aureus* has become an increasing factor. Clinically, patients with a secondary bacterial pneumonia often improve from their initial influenza and then subsequently worsen, as the secondary bacterial pneumonia worsens. Bacterial pneumonia following an influenza infection accounts for over 25% of all influenza-related deaths. Other complications of influenza include myositis, rhabdomylitis, encephalitis, transverse myelitis, and Guillain–Barré syndrome [2, 7].

As with complications from pneumonia, influenza mortality is highest in those with underlying comorbid disease or at the extremes of age. The elderly, particularly those in chronic care facilities, constitute the majority of deaths, followed by those over age 50 with underlying illnesses. Children under 1 year of age are the most vulnerable of the pediatric group [7].

4.2 Seasonal Influenza in Children

The incidence of influenza remains high in children, with 25–40% of school-aged children becoming infected each year. Uncomplicated influenza in children can present as in adults, but there is often more variability. Conjunctivitis, prolonged fever, oropharyngeal injection, nasal symptoms, and cervical adenopathy are more common. Additionally, respiratory symptoms, including shortness of breath, cough, and wheezing are increased. The clinical course for uncomplicated influenza in children is similar to adults, with symptoms usually resolving in 2–5 days [8].

As with adults, childhood complications from influenza usually occur in those with underlying medical conditions such as heart disease, congenital pulmonary disease (cystic fibrosis), hemoglobinopathies, and congenital metabolic abnormalities. Complications of influenza infection in children include pneumonia (both primary and secondary), otitis media, myositis, rhabdomyelitis, myocarditis, and neurological complications. Otitis media can occur in up to 50% of children with influenza. Secondary pneumonia can occur in healthy children as well as children with underlying conditions, and *Pneumococcus* and *Staphylococcus aureus* are the most common bacterial agents. Primary pneumonia is more common in children and can often be severe. The CDC began following severe pediatric cases of influenza in 2003, most of them manifested as pneumonia (23% were bacterial in nature). Half of these severe cases were in previously healthy children, and mortality was highest amongst those under age 6 months. Additionally, hospitalizations are higher among children when compared to adults, particularly for children under 6 months as well [8].

4.3 Avian Subtypes of Influenza A *in Humans*

The clinical manifestations of avian influenza in humans have ranged from mild conjunctivitis to severe pneumonia with multi-organ system failure. The median age of the cases in the 1997 HPAI H5N1 outbreak was 17.2 years, and, in the 2003–2006 Southeast Asian cases, it was 16 years (range 2 months to 90 years). The incubation period ranged from 2 to 8 days after contact with sick or dead birds. The predominant clinical findings appear to vary with each *Influenza A* subtype. For example, in the 2003 Netherlands outbreak (H7N7), where 92% of patients (82 of 89) presented with conjunctivitis and a minority had respiratory symptoms. However, with HPAI in Hong Kong in 1997, and in Southeast Asia currently, pneumonia progressing to multi-organ failure, ARDS, and death was the predominant finding. Reye's syndrome, pulmonary hemorrhage, and severe nausea, vomiting, and diarrhea can

occur in complicated cases. The clinical course of patients with HPAI H5N1 is rapid, with 68% of patients developing ARDS and multi-organ failure within 6 days of disease onset. The case fatality rate has ranged from 67 to 80%, depending on the series. Once patients reach the critical care unit, however, the mortality is 90%. The average time of death from disease onset is 9 to 10 days.

5 Diagnosis

The diagnosis of influenza ranges from recognition of clinical findings to viral isolation and subtype analysis. During a seasonal outbreak of influenza, clinical diagnosis by experienced clinicians has a relatively high degree of certainty. The findings of fever, cough, sore throat, and malaise have a positive predictive value of 79%. However, this predictive value is best in young adults, as the elderly and those with chronic underlying diseases may not present with traditional symptoms [7]. Additionally, sporadic cases of influenza (outside of the yearly season) are very difficult to differentiate from other respiratory illnesses. Thus, clinical findings are supportive, particularly in a seasonal outbreak, but cannot completely include or exclude the diagnosis of influenza [2, 9].

Therefore, a laboratory confirmation of influenza is the most reliable. Viral culture is the laboratory gold standard and is performed with nasal or oropharyngeal washes or with lower respiratory samples, such as bronchoalveolar lavage. Viral culture also allows for further subtype analysis if needed, but it does take 48–72 h and may not be well suited for immediate needs or initiation of medication administration. Rapid tests can be performed by immunofluorescence or enzyme immunoassays and have a sensitivity and specificity over 90% during seasonal outbreaks. Polymerase chain reaction-based assays are helpful for rapid diagnosis of new or avian subtypes and can additionally detect very low viral levels, which may be helpful after the initial 48 h of peak viral shedding. Finally, serology is helpful for retrospective analysis of exposure to certain strains or subtypes and is performed by complement fixation or enzyme-linked immunoabsorbant assay [9].

6 Treatment

Two classes of antiviral drugs, neuraminidase inhibitors and M2 inhibitors (adamantanes), are used for both the treatment and prevention of influenza. Due to resistance and side effects with the adamantanes, the neuraminidase inhibitors have become the mainstay of influenza antiviral treatment and prophylaxis [10].

6.1 Antivirals: Adamantanes

Amantadine and rimantadine are the two main drugs in the class of adamantanes (Table 4). These drugs target the M2 protein of *Influenza A*, which forms a protein

Table 4 Summary of antivirals for the treatment and prophylaxis of influenza

	Adamantanes	Neuraminidase inhibitors		
	Amantidine	Rimantidine	Oseltamivir	Zanamivir
Spectrum	Influenza A	Influenza A	Influenza A and B	Influenza A and B
Administration	Oral	Oral	Oral	Inhalation
Treatment dose	100 mg BID	200 mg QD	75 mg BID	10 mg BID
Prophylaxis dose	100 mg QD	100 mg QD	75 mg QD	10 mg QD
Side effects	Nausea, vomiting, CNS	Nausea, vomiting, CNS	Nausea, vomiting, psychiatric (children)	Bronchospasm, cough
Dose reduction	Renal dysfunction	Elderly	None	None
Generic	Yes	Yes	No	No
Pediatric indication	Yes (4–8 mg/kg/d)	Yes (5 mg/kg/d)	Over 1 year (1 mg/kg/d) for treatment and prophylaxis	Over age 8 (10 mg BID) for treatment, over age 5 for prophylaxis
Pregnancy schedule	C	C	C	C
Resistance in seasonal strains	Over 90%	Over 90%	1–5%	1%

BID, twice daily; CNS, central nervous system; QD, once daily.

channel in the viral membrane that is essential for efficient viral replication. By blocking this ion channel, the virus is unable to fuse with the host cell membrane and thus replication is stopped. The adamantanes only have activity against *Influenza A*, as *Influenza B* lacks the M2 protein. Initial studies performed in young adults showed that both amantadine and rimantadine decreased the length of symptoms of influenza by approximately 24 h [10]. Additionally, the severity of fever and malaise was also decreased during the study. There was no effect on overall mortality or the development of complicated influenza in initial studies.

Both amantadine and rimantadine reach peak serum levels approximately 1–2 h after initial dose. Serum concentration is slightly higher with rimantadine, which has a half-life elimination of approximately 36 h. In the elderly, amantadine reaches higher serum levels and has a longer half-life of 16 h when compared to young adults. Rimantidine is metabolized and excreted by the liver and thus must be dose-adjusted in hepatic dysfunction. Amantadine is excreted unmetabolized in the urine, and if the creatinine clearance is below 50 ml/min, the dose must be reduced [10, 11].

The adamantanes are well tolerated by young adults [11, 12]. However, especially in the elderly, central nervous system side effects are common. These include anxiety, insomnia, confusion, and hallucinations and are more prominent with

amantadine. Increased seizure activity in those with a prior history has occurred. Finally, anticholinergic side effects of dry mouth and worsening glaucoma have also been reported. In initial studies with amantadine, the discontinuation rate was 13–17% (4–8% with placebo), largely based on the neurological side effects. Both amantadine and rimantadine have teratogenic effects in rat animal models and thus are not used in pregnancy [11].

6.2 Antivirals: Neuroaminidase Inhibitors

Oseltamivir and zanamivir are the two neuraminidase inhibitors currently used for prophylaxis and treatment of influenza (Table 4). The neuraminidase inhibitors prevent the release of virions from the host cell by acting as sialic acid analogs. By binding to sialic acid, they prevent hemagglutinin from binding to uninfected cells as well as inhibit sialic acid cleavage of progeny virions, reducing further spread. Due to their mechanism of action as a sialic acid analog, neuraminidase inhibitors are active against both *Influenza A* and *Influenza B* viruses [2, 10].

For treatment, Zanamivir is given by dry powder inhaler at 10 mg twice daily. Approximately 13% of the dose is deposited in the distal tracheal and bronchi while the remaining 78% remains in the oropharynx. Zanamivir concentrations remain 1,000 times the viral IC50 at 12 h after dosing. The small amount of drug that enters the systemic system is excreted renally. However, due to the low levels, no adjustment for renal dysfunction is required. In clinical studies with zanamivir administered twice daily for 5 days, the median time to alleviation of influenza symptoms was 1 day shorter compared to placebo [12, 13]. This occurred for both *Influenza A* and *B* but was dependent on time of administration. Benefit was seen when zanamivir was given within 30 h of the onset of symptoms. No benefit was demonstrated if administered after 30 h. Studies in immunocompromised hosts and in patients with severe cases of influenza were not performed, so in those settings where viral shedding and disease may last beyond 48 h, zanamivir may have some theoretical benefit. In high-risk patients, the development of influenza complications, especially asthma and bacterial pneumonia, was also diminished. The major side effect of zanamivir was asthma and bronchospasm and thus the drug should be used with caution in those with underlying lung disease.

Oseltamivir has good bioavailability and is administered as either a capsule or powder (for liquid suspension) at 75–150 mg twice daily. Bioavailability is 80% with a wide body of distribution, and a 100 mg does yields serum levels of 250 ng/ml with a half-life of 8 h. The drug is renally excreted and a dose reduction is recommended for a creatinine clearance less than 30 ml/min. In multiple clinical trials, oseltamivir reduced the median duration of symptoms of influenza (fever, cough, malaise) by 1–2 days when given within 24 h of onset of symptoms. The reduction of symptoms appeared to be greater in laboratory-confirmed *Influenza A* when compared to *Influenza B*. Complications, including pneumonia, bronchitis, sinusitis, and otitis media, were lowered by as much as 50% in adults and children. Antibiotic

use also was reduced in the oseltamivir group. As with zanamivir, oseltamivir is well tolerated, with only 15% of patients reporting nausea. In the past few years, particularly in pediatric cases from Japan, delirium and self-injury, including suicide, have been reported [8, 10]. Oseltamivir is pregnancy category C and there is limited data on pregnant patients; however, in a rabbit model, minor skeletal changes have been reported [12, 13].

6.3 Antiviral Resistance

Influenza resistance to the adamantanes occurs rapidly and is currently widespread, limiting their use in treatment and prophylaxis. In fact, the CDC currently does not recommend the use of the adamantanes unless susceptibility is known, such as in a focal outbreak. Resistance to both amantadine and rimantadine occurs through a single point mutation, leading to high-level resistance that confers to the entire class. Initially, resistance sometimes developed during therapy, starting as early as day 2–3 of drug administration. However, most recently, the CDC reported that 92% of *Influenza A* (H3N2) isolates in 2006 were resistant to adamantanes [10, 11]. All of the resistant isolates had a substitution at codon 31 of the M2 protein. This widespread resistance has developed from adamantane overuse in the clinical settings as well as use in poultry outbreaks over the years, thus nearly rendering this class useless [14, 15].

Resistance in neuraminidase inhibitors appears to arise much more slowly and currently is significantly less, about 1–5% of isolates (Table 4) [15]. Resistance occurs with amino acid substitutions at either the NA or HA site. With NA mutations, a substitution of glutamine to glycine at position 119 in *Influenza A* and 117 in *Influenza B* results in decreased binding affinity at the NA active site. Cross-resistance is variable with this mutation, as resistance to oseltamivir was not conferred to zanamivir; when conferred, it has led to tenfold increase in the inhibitory concentration. Additionally, this mutation has yielded decreased viral infectivity and binding ability that was subsequently demonstrated in animal models [15]. Changes in the HA at or near the sialic acid binding site alter the viral binding and decrease the viral dependence on the NA. This change confers class resistance, as HA mutations to oseltamivir during treatment lead to a tenfold increase in the inhibitory concentrations of zanamivir. The development of resistance appears to be related to prolonged viral replication and shedding. In a few cases in high-risk patients (bone marrow transplant), therapy with oseltamivir led to resistance after receipt of the drug for 2 weeks, with two NA mutations and an M2 mutation conferring a 1,000-fold increase in zanamivir inhibitor concentrations. After therapy was terminated, the NA mutation disappeared but the M2 change persisted. Thus, therapy with prolonged viral shedding in certain hosts (e.g., immunocompromised) may lead to multiple mutations at the NA and HA sites, increasing resistance. However, thus far, there is no evidence that these mutations persist in the community [14, 15].

7 Prevention

7.1 Vaccine Basics

Influenza vaccination is the cornerstone of influenza prevention. Vaccine development, delivery, and administration to select groups can significantly impact the scope and severity of the influenza outbreak each season. Vaccine design and preparation are followed by targeted vaccination of high-risk groups and children, resulting in increased population immunity and a lower burden of disease. Human strains of *Influenza A* (H1N1, H3N2) and *Influenza B* circulate each year, and immunity develops from antibodies directed against the HA and NA surface glycoproteins. However, these glycoproteins vary each year (antigenic drift), making yearly vaccination paramount [16, 17].

As *Influenza A* and *B* undergo antigenic drift and shift, new variants emerge each year that are able to evade host immunity developed from vaccination or infection in prior years. Thus, worldwide surveillance of current strains is essential in order to estimate the most accurate HA and NA that will emerge the following year. Both the World Health Organization and the CDC estimate the strains available for vaccine development. Two major types of vaccines currently exist: an inactivated compound (TIV) and a live attenuated virus (LAIV). Both types of vaccines are trivalent, in that they contain the HA and NA for two *Influenza A* strains (H1N1, H3N2) and one *Influenza B* strain. The inactivated vaccine contains either whole virus or subvirion products, which are designed to ensure the presentation of a relevant HA and NA to the immune system. Inactivated influenza vaccine is given intramuscularly. The live attenuated virus is different as it is developed from a cold-adapted attenuated virus that contains the reassorted HA and NA of the selected strains. The LIV is administered by nasal mist spray and subsequently leads to replication of the virus in the distal upper respiratory tract (cold adaptation area). Thus, immunity develops through infection and subsequent antigen presentation [16, 17].

Vaccine manufacture takes approximately 6–9 months, so selection and development of influenza strains must begin in advance of the yearly influenza season. Therefore, vaccine mismatch can occur, reducing the efficacy of the vaccine and affecting the number and severity of influenza cases throughout the community. Additionally, developing a vaccine 6–9 months in advance means that policymakers must anticipate yearly usage, which can lead to shortages or extensive surpluses, depending on the year [16–18].

7.2 Vaccination in Adults

Vaccine efficacy depends largely on how closely the strain selected for the vaccine compares to the circulating strain during the yearly influenza season. Additionally, efficacy varies for the TIV and LAIV vaccines and according to the age of the individual and the presence or absence of underlying medical conditions. In a year when the vaccine and circulating strains are well matched, vaccine efficacy in healthy

adults can be up to 89% for *Influenza A* and 88% for *Influenza B* with the TIV. In years of a single strain mismatch, efficacy can drop to 50%. For the LAIV, reductions in febrile illness, respiratory illness, and missed workdays were significantly lower despite a mismatch between vaccine and circulating strains [16]. However, in a TIV-LAIV comparative trial, vaccine efficacy against serologically confirmed *Influenza A* was 74% for both TIV and LAIV, but TIV provided significantly better protection than LAIV for *Influenza B* (80% vs. 40%) [16, 18]. In a second trial conducted over 5 years, adults with *Influenza A* had 74% protection with TIV [16, 18]. With LAIV, 85% efficacy was noted with H1N1 subtype, but only 58% with H3N2. Both trials reported significant decreases in missed workdays, antibiotic use, and development of febrile illnesses, in addition to reducing serologically confirmed influenza [16, 18].

In high-risk groups, vaccination has shown additional benefits. In the elderly, vaccination efficacy has been reported to be as low as 50% [19], with outbreaks occurring in long-term care facilities among vaccinated individuals. However, vaccination is associated with significantly lower rates of hospitalization, pneumonia, and respiratory tract disease among these high-risk individuals. Mortality reduction in the elderly was not demonstrated in an individual study, but a meta-analysis suggested a slight reduction in the vaccination group [19]. Other at-risk groups, including patients with HIV infection or other chronic underlying diseases, receiving, immunosuppression, or experiencing pregnancy, have not been well studied in randomized trials and vaccine efficacy is more difficult to determine. However, due to their elevated risk for complicated influenza, vaccination is recommended in persons with these indications [19].

Adverse reactions vary for both the TIV and LAIV. Because the TIV is egg developed, allergy and anaphylaxis to egg protein can develop. Local reaction site inflammation and infection can also occur. An association between Guillain–Barré syndrome and influenza vaccination has been documented but was more prevalent with older preparations and with influenza infection itself [16]. The LAIV is also well tolerated, but due to its intranasal administration, rhinorrhea and nasal congestion are the most common side effects reported. In initial trials, wheezing, particularly in children under 4 months of age, was reported [16, 18]. Individuals with moderate to severe asthma were excluded from these studies.

The Advisory Committee on Immunization Practices at the CDC (Table 5) develops lists of targeted individuals for vaccination. Currently, these higher risk groups include those greater than 50 years of age, residents of a chronic care facility or nursing home, health-care providers, individuals with a chronic illness (pulmonary (including asthma), cardiovascular (excluding hypertension), renal, hepatic, hematologic, or metabolic disorders (including diabetes mellitus), or immunosuppression (including immunosuppression caused by medications or HIV infection)), and those who are pregnant. The LAIV is indicated for individuals aged 24 months to 49 years and should not be given to those patients with a chronic illness, pregnancy, history of Guillain–Barré syndrome, or immunosuppression. Thus, for individuals outside of the LAIV age group or with any contraindications, the TIV is the only form of vaccine indicated [18, 20].

Table 5 Targeted groups for influenza vaccination [18, 19]

Indication for vaccination	
Adults	Children
• Age > 50 years	• Age 6–59 months
• Resident of chronic or long-term facility (e.g., nursing home)	• Chronic and congenital pulmonary and cardiovascular disease (e.g., cystic fibrosis)
• Chronic illness (e.g., asthma, cardiovascular, renal, hepatic, hematologic, metabolic disorders (diabetes))	• Children on long-term aspirin therapy
• Immunosuppression (e.g., HIV, transplantation, medications)	• Children with difficulty controlling oral secretions (e.g., cognitive illness)
• Chronic neurologic disease (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, neuromuscular disorders)	• Metabolic and renal disorders
• Pregnancy during season	• Children in household of high-risk adult
• Health-care workers	• Healthy school children desiring vaccination
• Contacts of chronically ill	

7.3 Vaccination in Children

As for adults, vaccination efficacy in children is directly correlated with closeness in the match between the vaccine and seasonal strain [8, 18]. In studies with TIV, children over the age of 2 years had 59–65% protection against laboratory-confirmed influenza. In children under 36 months of age, efficacy appeared directly related to a history of prior influenza infection, as those with antibodies to *Influenza A* or *B* prior to vaccination developed a more robust response [16]. In addition to reduced rates of influenza infection, lower rates of otitis media and asthma exacerbation were also noted. Finally, children's immunity appeared to confer protection to other non-vaccinated household members, with an over 40% reduction in household members experiencing a febrile illness [21].

LAIV has efficacy rates of 30–93% depending on vaccine match, but with a close match, efficacy in children was around 93% [16]. Interestingly, protection in the second year after vaccination was 87%, even when the vaccine strain did not match, suggesting some increased protection against mismatched strains in children. As with TIV, cases of influenza acquired after vaccination were significantly milder. Multiple studies comparing LAIV to TIV in children show a 55% greater efficacy of LAIV than TIV, as assessed by laboratory-confirmed cases of *Influenza A*. Additional increased efficacy with LAIV in those with asthma (35%) and chronic respiratory infections (55%) was also noted. Finally, where vaccine mismatch occurred, LAIV was 35% efficacious while TIV provided no protection

[16, 18]. For *Influenza B*, the efficacy of LAIV and TIV was similar in these studies [38, 16, 18, 21].

The dosing for LAIV and TIV is different for children than for adults. The TIV dose is 0.5 ml intramuscularly and LAIV is 0.2 ml (0.1 ml per nostril). However, in children under 9 years of age, two doses of vaccine are recommended in the first year of vaccination, with only one dose needed in the years thereafter. Two doses provided optimal protection and efficacy (up to 93%); the first dose should be given a few months before the season, with the second dose 2–3 months after the first [8, 16, 18, 21].

The adverse events for TIV and LAIV are similar for children and adults. With TIV, local site reactions, including swelling, erythema, and pain can occur. Additionally, individuals with an egg allergy can develop anaphylaxis. Rash can also occur, and rarely seizures have been reported. Asthma exacerbations have not been associated with TIV. With LAIV, asthma exacerbations were initially thought to be associated, but post hoc analysis showed that the rates of asthma exacerbation in those with a history of mild asthma were similar in the two groups. Wheezing did initially appear to be increased among children aged 6–24 months in the LAIV group, along with hospitalization rates. However, further analysis suggested that medically significant wheezing and hospitalization were similar between the two groups. Overall, LAIV may increase the likelihood of wheezing but clinically significant asthma or hospital admission was not noted in the studies [8, 16, 18, 21, 22].

7.4 Antiviral Prophylaxis

Studies have been performed with both the adamantane and the neuraminidase classes of antivirals [10, 12]. Prior to the recent development of widespread resistance, the adamantanes provided adequate prophylaxis with a 50% reduction in laboratory-confirmed influenza and a 70% reduction in influenza-like illness when administered for 3–7 weeks. However, with the advent of widespread resistance, along with the efficacy and reduced side effects of the neuraminidase inhibitors, adamantanes are no longer recommended for prophylaxis. In certain situations, adamantanes may be indicated, such as in response to an outbreak in a chronic care facility where the virus is known to be susceptible to the drugs.

Both oseltamivir and zanamivir have been studied extensively for prophylaxis (Table 4). Oseltamivir has been approved for once daily use as prevention and has been studied in household contacts, nursing homes, and the general community. When given Oseltamivir at 75 mg daily for 7 weeks, healthy, unvaccinated adults had 75% fewer cases of influenza as compared to those given placebo. In studies evaluating household contacts of known influenza cases, a risk reduction of 59% was seen. Finally, during an outbreak in nursing home residents who were vaccinated, oseltamivir markedly reduced the rate of influenza development. Zanamivir, when compared to placebo, has been shown to decrease rates of laboratory-confirmed influenza (2% vs. 6%) when given to young, unvaccinated adults. In household

contacts, influenza significantly reduced the rates of influenza (4% vs. 16%) when compared to placebo. The drug was well tolerated in these studies and no emergence of resistance was noted. Thus, antiviral prophylaxis with neuraminidase inhibitors is indicated for seasonal influenza in patients unable to receive or respond effectively to vaccination, household contacts, and contacts in high-risk groups during an outbreak [10, 12, 13].

In regard to pandemic influenza, little is known about the efficacy of antiviral prophylaxis. Because a pandemic will come in multiple waves affecting different populations, targeted prophylaxis will be difficult. Strain type, resistance, and virulence may all effect susceptibility, and the necessary length of prophylaxis will be unknown. Thus, the need for large amounts of neuraminidase inhibitors will be a limiting factor in providing protection and prophylaxis to all members of the community. Targeted prophylaxis algorithms and plans will need to be used instead to lessen the burden of disease and focus on the highest risk members of the community [17].

Key Points

- *Influenza A* and *B* cause a yearly influenza outbreak with variable respiratory disease ranging from mild to severe. Complications and death are highest in the elderly, children under 6 months, and high-risk individuals.
- Due to genetic changes, new strains of influenza emerge constantly, thus creating the possibility of a pandemic. Additional changes in the last two decades include the increased infection in humans by avian subtypes with high morbidity and mortality.
- Treatment of influenza is supportive, and if given early, antiviral treatment can reduce symptom time and complications. Due to recent emergence of widespread resistance to adamantanes, only the neuraminidase inhibitor class is currently recommended for treatment.
- Vaccination against influenza is the mainstay for prevention, with the elderly, children, and high-risk groups recommended for vaccination. Both inactivated and live attenuated virus vaccines are available. Prophylaxis with neuraminidase inhibitors can provide protection in high-risk groups.

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Invasive Fungal Infections

Javeed Siddiqui

1 Introduction

Over the last 30 years, invasive fungal infections have been an increasing cause of morbidity and mortality in immunocompromised and immunocompetent patients. Currently, invasive candidiasis, specifically candidemia, represents the fourth most common nosocomial bloodstream infection [1]. Furthermore, major transplant centers are dealing with an increase in invasive aspergillosis in both allogeneic and autologous hematopoietic stem cell transplant patients.

A fundamental principle explaining why invasive fungal diseases occur is the concept that "nature abhors a vacuum." As we treat more patients with broader spectrum antibacterial agents, something has to fill the void – this tends to be either resistant bacteria or fungi. Given the current epidemiology, we can no longer expect that invasive fungal infections will occur only in significantly immunocompromised patients. Under the appropriate circumstances, any of our ICU, oncology, or post-transplantation patients could be at risk for invasive fungal infections.

In addition, there has been a clear shift in the species of *Candida* associated with invasive disease. No longer can we assume that all candidial infections are due to *Candida albicans*, as 50% or more of invasive candidiasis is now due to non-*albicans* species [2].

Advances in diagnostics beyond the traditional culture-based methodologies allow for more sophisticated identification and speciation of fungi. Laboratories now employ peptide nucleic acid fluorescent in situ hybridization (PNA-FISH) techniques for *Candida* species. A double-sandwich enzyme-linked immunosorbent assay for the detection of galactomannan and a PCR-based methodology is available to detect *Aspergillus*.

J. Siddiqui (✉)
Division of Infectious and Immunologic Diseases, School of Medicine, University of California Davis, Sacramento, CA, USA
e-mail: javeed.siddiqui@ucdmc.ucdavis.edu

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With regard to treatment, it is reasonable to say that we are now in a "golden age" of antifungal therapy. With the development of extended spectrum triazoles and echinocandins, we have truly changed the treatment paradigm for invasive candidiasis, aspergillosis, and other fungal infections. The recent approval of posaconazole now offers clinicians an additional option to treat invasive zygomycosis. Thus, the medical management of invasive mycosis is a dynamic field with increasing diagnostic and treatment options.

1.1 Fungi of Importance

Even though there are over a hundred thousand different species of yeasts and moulds occurring in the environment, the majority of medically relevant invasive mycoses involve a select number of organisms. The medically important yeasts include *Candida* species and *Cryptococcus* species. The medically relevant moulds include *Aspergillus* species, *Alternaria* species, *Bipolaris* species and *Curvularia* species (causing phaeohyphomycosis), *Fusarium* spp., *Pseudallescheria boydii* (*Scedosporium apiospermum*), *and Penicillium marneffei* (causing hyalohyphomycosis),and the Zygomycetes, which include *Mucor* species, *Rhizopus* species, *Rhizomucor* species and *Absidia* species. In addition, the dimorphic fungi include the prominent organisms responsible for endemic mycosis, i.e., *Coccidioides immitus*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans*.

1.2 Differences Between Bacteria and Fungi

A key taxonomy issue is the difference between bacteria and fungi. Bacteria are prokaryocytes and fungi are eukaryocytes. Bacteria are unicellular microorganisms whose shape is determined by their cell wall. The difference in their classification, gram positive or gram negative, is based on the staining properties of the individual cell walls. Microbiologically, bacteria grow best in a neutral pH (6.8–7.2) environment and often require limited assistance in terms of specialized media [3]. Fungi are nonmotile eukaryotic microorganisms that contain a nucleus, produce filamentous and branched structures, and have a cell wall that contains chitin or cellulose. Fungi prefer to grow in an acidic environment, pH (4.5–6.0), and require specific media and incubation at 25–30°C for optimal growth [3].

To further understand fungal taxonomy, it is essential to understand that fungi occur in two basic growth states:

- A unicellular or yeast form that is defined morphologically as a single-celled fungus that reproduces by simple budding to form a blastoconidia. Colonies are described as moist or mucoid. Yeast are classified as basidiomycetes such as *Cryptococcus* species or as ascomycetes such as *Candida* species.

- Moulds are large, complex multicellular organisms characterized by the production of hyphae with unique morphological characteristics that can assist their identification. Often there is confusion between the two common forms of the word – mold or mould. The word "mould" is derived from the Norse word meaning fuzzy, whereas the term "mold" is from the French derivative meaning a form or shape, such as a "plaster mold." From a medical viewpoint, the appropriate spelling is mould.

2 Candidial Infections

2.1 Taxonomic Classification

Kingdom: Fungi; Phylum: Ascomycota; Subphylum: Ascomycotina; Class: Ascomycetes; Order: Saccharomycetales; Family: Saccharomycetaceae; Genus: *Candida*

Candida species, which are yeasts, are the most common fungi involved in invasive human disease. These organisms occur abundantly in the human gastrointestinal tract and vagina. *Candida* species can be isolated in stool and from various mucus membranes where they exist as a commensal species. Although over 150 various species of *Candida* have been identified, the common species associated with medical mycosis are listed in Table 1 [4].

Table 1 Species commonly causing invasive candidiasis

Species name
C. albicans
C. glabrata
C. tropicalis
C. parapsilosis
C. krusei
C. lusitania
C. dubliniensis
C. guilliermondii

2.2 Epidemiology

Traditionally, physicians were concerned primarily with *C. albicans,* because it was the most common cause of candidiasis in humans. Due to myriad epidemiological factors, we can no longer regard invasive candidiasis as essentially always due to *C. albicans*. Today, standard of care dictates identifying *Candida* to the level of speciation. A clinician must be aware of which precise species of *Candida* is responsible for the infection, as various *Candida* species have differing antifungal resistance patterns.

2.2.1 Changing Epidemiology

Non-*albicans Candida* species increasingly cause nosocomial bloodstream infections. Data from the National Nosocomial Infections Surveillance System (NNIS) reveal that non-*albicans* species were responsible for only 24% of nosocomial fungal infections involving *Candida* species in the 1980s [4]. Within a decade, however, non-*albicans* species accounted for 46% of bloodstream infections due to *Candida* species, as shown by data from the SENTRY Antimicrobial Surveillance Program (1997–2000) [5]. Numerous other epidemiological surveys have documented the shift from predominately *C. albicans* to non-*albicans* species (Table 2) [2, 6].

Table 2 *Candida* species causing bloodstream infections

	Percent of infections reported (years studied)			
	Wingard et al. [18].	Rex et al. [19].	Nguyen et al. [20].	Pfalleret al. [5, 6].
	(1952–1992)	(1989–1993)	(1990–1994)	(1992–1998)
Candida species				
C. albicans	54	56	52	52
C. glabrata	8	13	16	18
C. parapsilosis	7	10	11	15
C. krusei	4	2	4	2
Candida spp	2	2	2	2

The shift in *Candida* toward non-*albicans* species is likely due at least in part to selective pressures imposed by the increased utilization of antifungal agents such as azoles. Previous exposure to azole derivatives such as fluconazole increases the probability of *C. glabrata* and *C. krusei* occurrence; absence of previous azole exposure is associated with the presence of *C. albicans* and *C. tropicalis*. In addition, other factors undoubtedly contribute: *C. glabrata* infections are associated with prolonged hospitalization, prior broad-spectrum antibacterial exposure, prior exposure to fluconazole, and often mixed fungal infection; occur predominantly nosocomially; and have a predilection for immunocompromised and/or debilitated hosts. *C. glabrata* patients typically have a longer duration of hospitalization compared to controls. *C. parapsilosis* infection is associated with use of central venous catheters, hyperalimentation, nosocomial infection, receipt of a BMT or solid organ transplant, and admission to a neonatal care unit. In one study, one third of candidemia cases in patients >70 years of age were due to *C. glabrata*, thus bringing forth the concept that increasing age may result in changing colonization. This, coupled with the above-mentioned changes in medical practice, could account for the shift in epidemiology toward *C. glabrata* [6].

The changing landscape of *Candida* species infection stresses the importance of clinicians knowing the specific epidemiology for the intensive care units (ICUs) and medical centers in which they work. Substantial variations can occur even between

ICUs in the same medical center; each ICU may have its own micro-climate with regard to *Candida* species (Table 3) [8].

Table 3 Difference in *Candida* bloodstream infections among intensive care units [8]

	C. albicans	*C. glabrata*	*C. parapsilosis*	*C. krusei*	*C. tropicalis*
SICU (%)	33	52	7	8	0
MICU (%)	46	24	7	2	21
CICU (%)	55	22	3	0	19
NSICU (%)	65	35	0	0	0
PICU (%)	65	28	6	1	0
NICU	40%	10%	46%	0%	1%

2.2.2 Patients at Risk for Developing Invasive Candidiasis

The patients classically at risk for invasive candidiasis are those receiving broad-spectrum antibacterials, experiencing immune suppression, and/or receiving intravenous total parenteral nutrition. The definition of immune suppression can be broad, including those patients on primary immune-suppressive agents and those who are intrinsically immunosuppressed secondary to diabetes mellitus, severe burns, or premature birth. Predisposing factors for invasive *Candida* infections include underlying conditions, immune deficiencies, and iatrogenic conditions. Examples of underlying conditions are the following: leukemia, lymphoma, bone marrow transplant, organ transplant, graft-versus-host disease, AIDS, primary immune disorders, gastrointestinal disease, diabetes mellitus, severe burns, premature birth, and intravenous drug abuse. Granulocytopenia represents the primary immune deficiency leading to invasive candidiasis, followed by alterations in T-cell-mediated immunity occurring in patients with HIV/AIDS. Finally, iatrogenic factors include chemotherapy, immunosuppressive agents for stem cell or solid organ transplantation, broad-spectrum antibiotics, high-dose corticosteroids, indwelling catheters, receipt of peritoneal dialysis, hemodialysis, prolonged hospitalization, and parenteral nutrition. Identifying patients who may have an increased risk of developing invasive candidiasis can aid the clinician in choosing optimal diagnostic techniques and possibly an accelerated initiation of appropriate therapy.

2.3 Diagnosis

Traditionally, the primary method of diagnosing candidemia has been the standard blood culture or the fungal blood culture. Despite its convenience and ease of use, it provides disappointing results, with a false-negative rate of 30–50% [7]. Recently, a new "non-culture" method has become commercially available that may offer an enhanced benefit over the routine blood culture.

The enzymatic assay for (1, 3)-beta-D glucan (Fungitell, Associates of Cape Cod, Inc., East Falmouth, MA), a specific component of the fungal cell wall, has demonstrated adequate sensitivity and specificity in recent clinical trials. Detection of

(1, 3)-beta-D glucan in such sterile fluid and blood can provide a more rapid diagnosis with an enhanced sensitivity and specificity of 70 and 87%, respectively.

Diagnosis requires not only identifying *Candida* but also properly speciating the organism. As such, traditional methodology is time consuming, first requiring the identification of *Candida*, then an additional 24 h to perform the germ tube, and possibly an additional 72 h for speciation. Again, recent advancements in speciation techniques with in situ hybridization and new agar materials are likely to assist the clinician in timely diagnosis.

3 Aspergillosis

3.1 Taxonomic Classification

Kingdom: Fungi; Phylum: Ascomycota; Class: Eurotiomycetes; Order: Eurotiales; Family: Trichocomaceae; Genus: *Aspergillus*

Aspergillus species are filamentous, ubiquitous fungi found abundantly in soil and plant debris. The genus *Aspergillus* includes over 185 identified species, with approximately 20 species known to cause disease in humans. The common species associated with medical mycosis include the following: *A. flavus*, *A. terreus*, and *A. fumigatus*.

3.2 Pathophysiology

Aspergillus species can cause an array of human diseases. The key predisposing factor for invasive aspergillosis is immunosuppression, specifically granulocytopenia. Typically, when we are exposed to blown dust, we inhale inactive conidia of *Aspergillus* species, which due to their size of 3–5 microns can lodge in the lower respiratory tract. The conidia then can swell and shed their outer coat. At this stage, normal macrophage function can block further progression of *Aspergillus* species to prevent invasive disease. However, if a patient has compromised macrophage function, then the conidia can germinate into hyphae. Again, the body's neutrophils can block this phase of disease progression; however, if there is a lack of neutrophils, the hyphae invade the lung parenchyma and systemic vessels, thereby completing the final stage of invasive disease. Primary pulmonary disease caused by *Aspergillus* traditionally manifests as invasive pneumonia or as allergic bronchopulmonary aspergillosis. Although they have a common site of infection, the two diseases represent opposite ends of the spectrum. Invasive aspergillosis is rapidly progressive, often fatal, and usually occurs in patients with profound and sustained granulocytopenia. On the other hand, allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to *A. fumigatus* colonization of the tracheobronchial tree, which usually occurs in patients with asthma and/or cystic fibrosis and does not represent invasive disease. Despite the fact that *Aspergillus* species have a predilection for angioinvasion, it is rare to have positive blood cultures.

3.3 Diagnosis

Historically, invasive aspergillosis had mortality rates on average of 60% [8]. Diagnosis has been difficult, with cultures requiring long incubation times and yielding limited results. New methodologies of diagnosis may have a substantial impact on the overall management of invasive aspergillosis.

3.3.1 Galactomannan

Galactomannan is a polysaccharide component of the cell wall of *Aspergillus* species that is released into the circulation during invasive aspergillosis. The galactomannan antigen test is a non-culture based diagnostic technique detecting the presence of a specific fungal antigen in sterile body fluid. The commercially available galactomannan assay, Platelia Aspergillus EIA (Bio-Rad Laboratories), is a one-stage immunoenzymatic sandwich microplate assay that utilizes rat monoclonal antibody EBA-2 to detect circulating galactomannan antigen. In contrast to traditional culture-based methodologies, results from the galactomannan assay can be available in 3 h. Galactomannan antigen can be detected on average 7 days prior to the development of clinical signs in 65.2% of patients studied [9]. The assay is best suited as a screening test for patients at high risk of developing invasive aspergillosis. Three serial assays, every 48–72 h, should be obtained in order to maximize the potential benefits of the test. A positive result supports the diagnosis of invasive aspergillosis.

3.3.2 Diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA)

Clinical and laboratory diagnostic criteria for ABPA include the following: (1) clinical deterioration, including cough, wheeze, increased sputum production, diminished exercise tolerance, or diminished pulmonary function; (2) total serum IgE level greater than 1,000 IU/ml or greater than twofold rise from baseline; (3) positive serology results for *Aspergillus* species (*Aspergillus* precipitins or *Aspergillus*-specific IgG or IgE); and (4) new infiltrates on chest radiographs or a computed tomography (CT) scans. In addition, treatment for ABPA is also recommended in patients with cystic fibrosis who have new radiographic findings and symptoms and a change in baseline IgE level to greater than 500 IU/ml.

3.3.3 Imaging Studies

To evaluate a patient for invasive aspergillosis, a chest radiograph is usually the initial imaging study. However, often a chest radiograph is non-diagnostic or abnormal, offering limited insight into the disease process. As such, a CT scan of the chest, or more appropriately a high-resolution computed tomography scan (HRCT), can frequently provide important information about the patient's disease.

HRCT can identify lung pathology including solitary or multiple nodules, cavitary lesions, or alveolar infiltrates, with the characteristic halo sign (an area of

ground-glass infiltrate surrounding nodular densities). Additional features of invasive aspergillosis include a crescent of air surrounding nodules, which are indicative of a cavitation, or a wedge-shaped, pleural-based, and cavitary lesion that is consistent with pulmonary infarction. As such, many clinicians believe that it is reasonable to forego the chest radiograph and proceed directly to HRCT in patients suspected of having *Aspergillus* pneumonia.

In contrast, imaging studies of patients with ABPA demonstrate variable manifestations, ranging from fleeting pulmonary infiltrates to mucoid impaction to central bronchiectasis. Again, HRCT of the chest may further elucidate areas of bronchiectasis or lobulated infiltrates.

4 *Coccidioides immitis* and *Coccidioides posadasii*

4.1 Taxonomic Classification

Kingdom: Fungi; Phylum: Ascomycota; Class: Euascomycetes; Order: Onygenales; Family: Onygenaceae; Genus: *Coccidioides*

Coccidioides immitis and *C. posadasii* are dimorphic fungi found in soil of the Western Hemisphere from latitudes 40° north to 40° south. *C. immitis* is found predominately in California's San Joaquin Valley whereas *C. posadasii* occurs in the desert southwest of the United States, Mexico, and South America. However, the two species coexist in the desert southwest of the United States and Mexico. Although the two species are morphologically identical, they are genetically and epidemiologically diverse. The organisms are referred to as dimorphic fungi due to their morphological variability. The organisms grow in the mould form in soil, forming arthroconidia within the hyphae. The arthroconidia break off when the wind blows or when the soil is disrupted by humans, by animals, or by machines. Once released into the atmosphere, the arthroconidia are inhaled and the host is then subsequently infected. Once lodged in the respiratory tract, the arthroconidia undergo morphologic changes and develop into a spherule. For the next 48–72 h, the spherules then undergo repeated internal divisions until they are filled to capacity with thousands of endospores. Once they have reached a critical mass, the spherules rupture, releasing the endospores to continue to propagate the infectious process.

4.2 Epidemiology

In the United States, an estimated 100,000 patients develop coccidioidomycosis annually. In the Central California region known as the San Joaquin Valley, prevalence studies have estimated that approximately 24% of the population has been infected with *C. immitis* [10]. Of the individuals infected, approximately 60% are asymptomatic. In symptomatic individuals, 90% will experience flu-like illness that resolves without specific treatment. The remaining 10% of patients

develop severe chronic pulmonary or extra-pulmonary disease [10]. Predisposing risk factors for invasive disease include male gender, an immunocompromised state, pregnancy, diabetes mellitus, older age group, and African, Asian, or Filipino ancestry. It is possible that there may be a genetic predisposition to developing symptomatic coccidioidomycosis. The HLA class II DRB1*1301 allele marks a genetic predisposition to developing disseminated disease. This HLA haplotype may interfere with coccidioidal antigen presentation to T cells, thereby interfering with the body's immune response to control the organism and to prevent disease progression.

4.3 Diagnosis

The diagnosis of coccidioidal infection is best made through either serum or cerebral spinal fluid serology. The immunodiffusion IgM antibody appears early in infection and is usually detected as a precipitating antibody. Within weeks to months of a primary infection, the complement fixation antibody, corresponding to the IgG level, is measurable. When present, this titer can then be followed as a marker of disease progression or successful treatment. For example, an increasing complement fixation titer in the presence of therapy would indicate inadequate dosing or patient noncompliance and disease progression.

When necessary, culture and histopathological straining remain valuable options for the diagnosis of invasive coccidioidal infection. When submitting a specimen to the microbiology laboratory, clinicians should inform the staff that they suspect coccidioidal infection, as a number of laboratory personnel through the years have been iatrogenically exposed.

5 Histoplasma Capsulatum

5.1 Taxonomic Classification

Kingdom: Fungi; Phylum: Ascomycota; Class: Ascomycetes; Order: Onygenales; Family: Onygenaceae; Genus: *Histoplasma*; Specific descriptor: *capsulatum*.

5.2 Epidemiology

Histoplasmosis is a disease caused by the dimorphic endemic fungi *Histoplasma capsulatum* var. *capsulatum*. *H. capsulatum* is found in soils throughout the world. In the United States, the fungus is endemic in central and eastern states along the St. Lawrence, Ohio, Mississippi, and the Rio Grande rivers. The fungus grows best in soils that have a higher nitrogen content, specifically those enriched with bird or bat droppings. *Histoplasma* is a thermally dimorphic fungi existing as a mycelium in the environment but changing to a yeast once in the body and exposed to 37˚C. The

organisms enter the host as a microconidia via inhalation, lodging in the alveolar space and then budding into a yeast cell.

In immunocompetent individuals, histoplasmosis can be asymptomatic or can present as a mild, flu-like respiratory illness accompanied by fever, cough, malaise, shortness of breath, myalgias and arthalgias. In immunocompromised patients, histoplasmosis can result in disseminated disease with fungemia and end organ damage, including manifestation of hepatosplenomegaly.

5.3 Diagnosis

Diagnosis of invasive histoplasmosis can be effectively made using serum and urine antigen detection methodologies. In patients with disseminated disease, the urine antigen has been accurate in 90% of cases. Blood cultures and an examination of the peripheral smear may also provide valuable clinical clues in these patients.

6 Blastomyces Dermatitidis

6.1 Taxonomic Classification

Kingdom: Fungi; Phylum Ascomycota; Class: Ascomycetes; Subclass: Incertae sedis; Order: Incertae sedis; Family: Incertae sedis; Genus: *Blastomyces.*

6.2 Epidemiology

Blastomyces is an endemic, dimorphic fungi found in the Mississippi and Ohio river valleys and the northern regions of the United States. It is dimorphic because it is able to exist in a mould-like state at 25°C and a yeast-like state at 37°C. Humans are infected by inhaling the mould organisms following disruption of soil. Once lodged in the pulmonary tree, the organisms undergo a phase transition to the pathogenic yeast form. This morphological transition is an essential feature of the pathogenicity of *Blastomyces*. The organism can then multiply within the lung parenchyma and disseminate throughout the body. Primarily disseminated disease occurs in immunocompromised individuals, whereas localized disease tends to occur in immunocompetent patients. Pulmonary blastomycosis most commonly involves the upper and middle lobes, with a clinical presentation ranging from asymptomatic disease to mild pneumonia to acute respiratory distress syndrome [11]. Patients may present with fever, cough, myalgias, pleuritic chest pain, and occasionally with hemoptysis.

In contrast, cutaneous blastomycosis results from direct inoculation of the organism into the skin. Clinical presentation of cutaneous disease ranges from nodular lesions, which may begin as small pustules, to chronic non-healing ulcerations.

6.3 Diagnosis

Diagnosis can be established through direct examination of tissue or via a urine antigen test. Microscopic examination of tissue reveals the presence of the characteristic broad-based budding yeast. The commercially available urine antigen test demonstrates a high degree of sensitivity. Some case reports have indicated the utility of the urine antigen test as tool to monitor treatment response in patients with disseminated disease [11].

7 Cryptococcus Neoformans

7.1 Taxonomic Classification

Kingdom: Fungi; Phylum: Basidiomycota; Class: Urediniomycetes; Order: Sporidiales; Family: Sporidiobolaceae; Genus: *Cryptococcus*; Species: *C. gattii*, *C. neoformans* var. *neoformans*, *C. neoformans* var. *grubii*.

7.2 Epidemiology

Cryptococcus neoformans is a fungi that grows like a yeast and replicates by budding. Under optimal conditions *C. neoformans* can grow as a filamentous fungus. When existing as a yeast, it has a distinctive polysaccharide capsule. The species is composed of three variants (v.): *C. neoformans* v. *gattii*, v. *grubii*, and v. *neoformans*. The variants *C. neoformans* v. *grubii* and v. *neoformans* have a worldwide distribution and are often found in soil that has been contaminated by bird excrement. *C. neoformans* v. *gattii* is found mostly in the tropics, but it has also been confirmed on southern Vancouver Island on the southwestern coast of Canada [12].

Disease presentations associated with *Cryptococcus* include pneumonia, fungemia, and central nervous system disease. Older immunocompetent patients may present with a chronic pneumonia. The incidence of disease secondary to *Cryptococcus* increased with the emergence of the HIV/AIDS epidemic. As patients' T-cell functions deteriorate, they become susceptible to invasive *Cryptococcus* infection. HIV/AIDS patients develop pneumonia with fungemia and subsequently central nervous system disease. Often, cryptococcus meningitis is an AIDS-presenting illness.

7.3 Diagnosis

Invasive *Cyptococcus* can be identified by direct examination of cerebral spinal fluid, sputa, or bronchoalveolar lavage. Specimens are stained with an India ink preparation. Under high power, the India ink preparation shows a thick polysaccharide capsule surrounding the yeast. When performed by an experienced

microbiologist, India ink methodologies can be used to diagnose disease in 25–50% of patients with cryptococcal meningitis. *C. neoformans* can be cultured using standard fungal culture media, Sabouraud dextrose agar. Rapid diagnosis is based on serological testing using a latex agglutination test to detect the cryptococcal polysaccharide in serum and CSF; this test is extremely sensitive in patients with meningitis [12]. In addition, serologic testing can be an effective and useful tool in ongoing management of the disease. By following the decrease or rise in serologic titers, clinicians can quantitatively monitor the effectiveness of treatment.

8 Treatment Strategies and Options

We are currently in the "golden age" of antifungal therapy. No longer are we limited to the use of one or two medications with incomplete efficacy and wide ranging toxicities. Lipid formulations of polyenes, echinocandins, and extended spectrum triazoles are now available and have dramatically expanded the antifungal armamentarium. As clinicians, we need to demonstrate good antimicrobial stewardship and carefully choose treatments that best fit with the appropriate spectrum of activity, have a favorable resistance profile, and pose limited risk of toxicities for the patient.

8.1 Azoles

This class of antifungal agents works by inhibiting the cytochrome P450 14a-demethylase pathway. Azoles are fungistatic drugs that are available in both oral and intravenous formulations with the exception of posaconazole, which is only available in an oral suspension. The most commonly used azoles are: fluconazole, itraconazole, voriconazole, and posaconazole. Dosing for these agents must be adjusted based on the patient's creatinine clearance. Their primary toxicities are secondary to hepatic inflammation.

8.1.1 Fluconazole

Fluconazole is the first triazole that was highly effective and tolerable; it is available in both oral and intravenous formulations. Fluconazole is effective in the treatment of *Candida* species, with the exception of *C. krusei*, and is effective against *Cryptococcus* species and *Coccidioides* species. Fluconazole has a wide dose ranging scheme from 200 to 1,600 mg/day, with the appropriate dosing dependent on the organism and the site of infection. Of note, the oral formulation of fluconazole has approximately 97% bioavailability.

8.1.2 Voriconazole

Voriconazole is an extended spectrum triazole; the others extended spectrum triazoles are posaconazole and itraconazole. (Fluconazole and ketoconazole are considered traditional triazoles as they have a limited spectrum of activity.) Voriconazole comes in both intravenous and oral preparations. For intravenous voriconazole, the standard loading dose is 6 mg/kg q12h × 2 doses, followed by a maintenance dose of 4 mg/kg q12h. For patients taking an oral dose who are ≥40 kg, the loading dose is 400 mg q12h × 2 doses. For patients taking an oral dose who are <40 kg, the loading dose is 200 mg q12h × 2 doses and the maintenance dose is 100 mg q12h.

In vitro, voriconazole demonstrates activity against *Candida* species, *Aspergillus*, the phaeohyphomycoses: *Alternaria* species, *Bipolaris* species, and *Curvularia* species and the hyalohyphomycoses: *Fusarium* spp. *Pseudoallescheria boydii* (*Scedosporium apiospermum*) and *Penicillium marneffei*. Voriconazole does not demonstrate activity against the *Zygomycetes* species.

Limitations of voriconazole are its extensive cytochrome P450 interaction, specifically 2C19, 2C9, and 3A4. Patients with invasive fungal infections not responding to therapy had low voriconazole blood levels in one study, which emphasizes the need to monitor voriconazole levels in patients regardless of the route of administration [13]. The primary toxicity of voriconazole is photopsia, the presence of perceived flashes of light, which occur within 2 h of administration. It has been determined that photopsia does not result in long-term effects or toxicities.

8.1.3 Posaconazole

The newest of the extended spectrum triazoles to be available is posaconazole. The standard dosing of posaconazole is 200 mg three times a day when used for prophylaxis and 400 mg two times a day when used for treatment. Posaconazole is only available in an oral suspension and should be administered with food or a nutritional supplement. In vitro, posaconazole demonstrates activity against *Candida* species, *Aspergillus* species, and the *Zygomycetes* species.

Randomized clinical trials have demonstrated posaconazole to be an effective option for prophylaxis of fungal infection in patients with acute leukemia undergoing chemotherapy [14].

8.1.4 Itraconazole

Itraconazole is a triazole antifungal with activity against most species of *Candida*, *Aspergillus*, *Coccidioides*, *Histoplasma*, and *Blastomyces*. Its mechanism of action is identical to the other triazoles in its inhibition of the fungal cytochrome P450 oxidase-mediated synthesis of ergosterol. Itraconazole is approximately 99% protein bound and thus may not have effective central nervous system concentration and thereby should not routinely be used for the treatment of meningitis. Itraconazole is dosed 200–400 mg daily. The drug displays nonlinear pharmacokinetics; as

such, slight dose modifications may result in substantial increases in drug concentration. Itraconazole is available in a capsule formulation, liquid suspension, and intravenous formulation. A key issue with the capsule formulation is gastric acid that is needed to facilitate absorption of the drug. Itraconazole capsules may be taken with food, orange juice, or a cola drink to enhance gastric acid production. However, despite these measures, issues with erratic absorption and varying degrees of bioavailability have complicated the use of itraconazole capsules. These absorption issues are of much less concern with the oral suspension. Itraconazole oral suspension has improved absorption and is not significantly affected by gastric acid. Of note, the oral suspension contains cyclodextrin, which can be associated with an osmotic diarrhea. The intravenous formulation of itraconazole also contains cyclodextrin and is thereby not indicated in patients with a creatinine clearance less than 30 ml/min. In addition to the hepatic toxicities found with all triazole antifungals, itraconazole has displayed negative inotropic effects and should be used in caution in those patients with underlying cardiac disease.

8.2 Polyene Antifungals

The polyene antifungals are agents composed of alternating conjugated double bonds that constitute a part of their macrolide ring structure. The agents within this class include nystatin, amphotericin B, and pimaricin. These agents interact with ergosterol in fungal cell membranes to form porin channels through the membrane, resulting in a loss of cellular content and cellular death.

8.2.1 Amphotericin B

Initially developed in the 1960s, amphotericin B has been the mainstay of antifungal therapy. Amphotericin B occurs in three primary preparations: amphotericin B deoxycholate, amphotericin B lipid complex, and amphotericin B liposome.

The primary toxicities associated with amphotericin B are renal and systemic [14]. Upon infusion, amphotericin B results in an acute phase cytokinemia due to increased levels of TNF-alpha, IL-6, IL-1, and prostaglandin E [15]. Patients can develop fever, chills, nausea, vomiting, and headache. These infusion-related toxicities can be decreased by premedicating with acetaminophen and/or diphenhydramine. The rate-limiting effects of amphotericin B are its renal toxicities. Amphotericin B results in a decrease in glomerular filtration due to constriction of the afferent arterioles, and continued use results in a type 1 renal tubular acidosis [16]. The impact and extent of decreased renal blood flow can be attenuated by prehydration, if clinically feasible, and renal tubular acidosis should be managed with replacement of magnesium and potassium [16]. Although the lipid formulations of amphotericin B have less toxicity, clinicians must monitor all patients receiving amphotericin B closely for evidence of nephrotoxicity.

Amphotericin B can be used in the treatment of invasive candidiasis, aspergillosis, zygomycosis, and endemic fungal infections (Table 4).

Table 4 Amphotericin B dosages for candidal infections

Preparation	Dose
Amphotericin B deoxycholate	0.5–1 mg/kg
Amphotericin B lipid complex	5 mg/kg
Amphotericin B liposome	3–5 mg/kg

8.3 Echinocandins

Echinocandins are a new class of antifungals that demonstrate fungicidal activity with a low toxicity profile. In contrast to polyene or triazoles, which both work at the level of the cell membrane, echinocandins offer a novel mechanism of action by inhibiting (1,3)-beta-D glucan, a component of the fungal cell wall. Currently, three members of the echinocandin class are commercially available, caspofungin, micafungin, and anidulafungin. They have not demonstrated rate-limiting toxicities, but isolated case reports have indicated possible elevation of hepatic enzymes. Dosing for the three agents is listed in Table 5.

Table 5 Echinocandins dosages

Drug	Loading dose	Maintenance dose
Caspofungin	70 mg IV (1 dose)	50 mg IV daily
Anidulafungin	200 mg IV (1 dose)	100 mg IV daily
Micafungin	N/A	100–150 mg IV daily

8.4 Treatment of Invasive Candidiasis

There are several options for the treatment of invasive candidiasis: triazoles (fluconazole), polyenes (amphotericin B), and echinocandins (caspofungin, micafungin, anidulafungin). Although all these agents have activity against *C. albicans*, their utility in the non-*albicans* species is varied. Each drug has its strengths and weakness and in order to optimize the likelihood of success, the clinician must weigh the balance among those qualities.

8.4.1 Fluconazole

Traditional dosing of fluconazole for most *Candida* infections has been a single 200 mg loading dose followed by 100 mg daily maintenance dose. But for candidemia, this may be a suboptimal dosing scheme. For candidemia, many clinicians elect to elevate the dose to a 400 mg loading dose followed by 200 mg daily maintenance dose. However this does not apply for *C. glabrata. C. glabrata's* susceptibility to fluconazole is dependent upon the dose, an attribute known as "susceptible dose dependent." As *C. glabrata* has an average fluconazole MIC of 32 ug/ml, a loading

dose of 800 mg followed by a maintenance dose of 400 mg per day should produce steady levels of 40 ug/ml, sufficient for effective treatment.

Complicating the treatment paradigm is data that some *C. glabrata* may be developing absolute resistance to fluconazole with a MIC > 64 ug/ml [17]. Accordingly, clinicians must be aware of their own hospital's resistance data and may choose to defer the use of fluconazole until resistance data on a specific isolate is available. Of note, *C. krusei* is intrinsically resistant to fluconazole and thus this drug should not be considered as a treatment option.

8.4.2 Amphotericin B and Candidiasis

In the case of candidial infection, amphotericin B has long been considered the "gold standard." In vitro, amphotericin B has activity against most species of *Candida*. The notable exceptions are *C. lusitaniae*, which is intrinsically resistant to amphotericin B, and *C. guilliermondii*, which has been shown to develop resistance to amphotericin B and empirically should not be considered susceptible. Although *C. glabrata* was once thought to be uniformly susceptible to amphotericin B, one study found that 25% of the isolates demonstrated resistance to amphotericin B [18]. The treatment of *C. glabrata* can be challenging and should be customized based on the hospitals local resistance data.

8.4.3 Echinocandins and Candidiasis

Echinocandins possess activity against all species of *Candida*, including *C. krusei* and *C. glabrata*. In vitro data indicates that the echinocandins demonstrate fungicidal activity against all *Candida* species. Caspofungin, micafungin, and anidulafungin have all been evaluated in randomized, blinded, noninferiority clinical trials for the treatment of candidemia. Based on the results of the above trials, expanding clinical experience, the medication's fungicidal activity and minimal toxicity; echinocandins represent an effective first line treatment option.

8.5 Treatment of Aspergillosis

With the expansion of antifungal agents, several new treatment strategies have emerged for patients with invasive aspergillosis.

8.5.1 Amphotericin B

For over 45 years, amphotericin B deoxycholate has been the mainstay of treatment for the management of invasive aspergillosis. The limitations have been its side effect profile and less than adequate response rates. A revolution in the application of amphotericin B occurred with the advent of lipid-based formulations. The lipid preparations allow for increased drug exposure and a reduced toxicity profile.

Dosing of the lipid preparations for the treatment of invasive *Aspergillus* species can vary: ambisome is given at 5–10 mg/kg per day and abelcet at 5–7 mg/kg per day.

8.5.2 Itraconazole

In clinical trials, itraconazole has demonstrated approximately 50% efficacy in the treatment of invasive aspergillosis [19].

8.5.3 Voriconazole

Few clinical trials have reshaped the treatment landscape as much as the "Global Comparative Aspergillosis Study," which evaluated the efficacy of voriconazole [20]. This study is the largest prospective, randomized, open-label, comparative trial of primary therapy for invasive aspergillosis to date. Conducted in 95 centers worldwide, the study compared voriconazole (6 mg/kg q12h day 1, then 4 mg/kg q12h) to amphotericin B deoxycholate (1.0–1.5 mg/kg/day). A significantly higher proportion of patients in the voriconazole arm had a successful response – 53%, compared with 32% in the amphotericin B arm after 12 weeks. Successful response required complete or partial resolution of all attributable symptoms, signs, and radiographic abnormalities present at baseline. Given the above data, voriconazole is now regarded by many clinicians as the drug of choice for the treatment of invasive aspergillosis.

8.5.4 Posaconazole

Posaconazole, an extended spectrum triazole, is the latest agent to be approved for the treatment of invasive fungal infections (IFI). Posaconazole is approved for prophylaxis in immunocompromised patients for the prevention of invasive *Aspergillus* and *Candida* infections. Two randomized clinical trials have demonstrated the efficacy of posaconazole (200 mg PO tid) in preventing invasive fungal infections as compared to standard triazole therapy (fluconazole or itraconazole) in immunocompromised patients with neutropenia [21, 22]. Proven or probable IFI were diagnosed in 2% of patients receiving posaconazole in comparison to 8% in the comparison group [21, 22]. The majority of breakthrough fungal infections in the fluconazole/itraconazole group were due to aspergillosis [21].

Posaconazole has also been investigated as salvage therapy for aspergillosis [23]. In these patients, the overall response to posaconazole therapy (800 mg/day divided doses) was 42%; compared to 26% in patients on "standard of care" therapy. The clear role of posaconazole in aspergillosis needs to be further defined, but its approval offers an enhancement to our overall antifungal armamentarium.

8.5.5 Echinocandins

The echinocandins offer a new option for the treatment of invasive aspergillosis. Caspofungin is the only echinocandin approved for the treatment of refractory

or intolerant invasive aspergillosis. In one clinical trial involving patients failing initial therapy for invasive aspergillosis, caspofungin demonstrated an approximately 45% clinical response [24]. Limited clinical data are available regarding the use of the remaining echinocandins, micafungin and anidulafungin, for aspergillosis. Mechanistically, the echinocandins impact the apical segments of *Aspergillus* species, thus conveying a "static" effect. Animal model studies have suggested that *Aspergillus* species remain viable despite exposure to an echinocandin. As such, the question arises whether echinocandins are appropriate as monotherapy for invasive aspergillosis but clearly opens the door for the concept of combinations antifungal therapy.

8.5.6 Combination Antifungal Therapy

Few concepts in infectious diseases have polarized physicians as much as the concept of combination therapy in the management of invasive aspergillosis. To date there has not been a randomized clinical trial to determine the efficacy of combination vs. monotherapy in invasive aspergillosis. Despite this shortfall, several in vitro and animal model studies have suggested benefits of combining antifungal agents that work at different sites within the organisms. As previously discussed, the echinocandins' site of action is the fungal cell wall, the triazoles function at the cell membrane level, and the polyenes also work at the cell membrane level. The basic principle of combination antifungal therapy is to combine agents with complementary sites of actions. As such, combining an azole and a polyene may not provide an enhanced benefit over monotherapy, because both agents function at the level of the cell membrane. In contrast, combining an echinocandin with either a polyene or a triazole attacks the organism at both the cell wall and the cell membrane, respectively. Among the most impressive studies of combination antifungal therapy was the salvage therapy trial published by Marr and colleagues [25]. This study focused on 47 patients with proven or probable invasive aspergillosis who were receiving voriconazole for salvage therapy. Subsequently, the salvage regimen was then augmented to the combination of caspofungin and voriconazole. Patients receiving the combination of caspofungin and voriconazole displayed a greater 3 months survival from both time of diagnosis and time of therapy. In addition, the probability of death was lower in patients receiving combination antifungal therapy in comparison to the monotherapy cohort. Further studies are needed to clearly elucidate the role of combination antifungal therapy for invasive aspergillosis.

8.6 Treatment of Coccidioidal Infection

Prior to the late 1980s, polyenes were the mainstays of treatment for invasive coccidioidal infection. With the advent of fluconazole, the management of coccidioidal infection has been revolutionized. In utilizing fluconazole, the starting dose is based on the site of infection. In the case of primary pulmonary coccidioidal infection, most physicians initiate fluconazole therapy at 200–400 mg per day. In comparison, coccidioidal meningitis would likely mandate a minimum of 800 mg of fluconazole

per day. The key to fluconazole therapy is evaluation of subsequent complement fixation titers to monitor treatment success or failure. In the realm of coccidioidal infection, fluconazole demonstrates a wide therapeutic window ranging from 200 to 1,600 mg/day in the setting of a normal creatinine clearance.

Amphotericin B deoxycholate continues to have a role in the treatment of coccidioidal infection. Experienced clinicians remain steadfast that in the presence of coccidioidal meningitis, the intrathecal administration of amphotericin B deoxycholate offers a therapeutic advantage. In addition, anecdotal case presentations have been reported suggesting an advantage of intrathecal amphotericin B in patients who develop central nervous system vasculitis secondary to coccidioidal meningitis.

Finally, posaconazole may have an emerging role in the treatment of patients with disseminated coccidioidal infection. A recently published open labeled clinical trial administered posaconazole, 800 mg/d, in divided doses, to patients known to be refractory to previous antifungal therapy [26]. Most of the patients were refractory to regimens including amphotericin B with or without the presence of an azole. At the conclusion of the trial, 73% of patients had demonstrated a successful response. Further studies need to be conducted in order to clearly define the role of posaconazole in the management of coccidioidal infection.

8.7 Treatment of Histoplasmosis

The polyenes, i.e., amphotericin B, have been the mainstay of therapy in patients with disseminated disease. Standard doses of deoxycholate and lipid formulation may be used; however, higher doses, such as 7.5–10 mg/kg/day, should be considered in patients with central nervous system disease.

Itraconazole has been considered for mild primary pulmonary disease, chronic pulmonary disease, and as consolidation phase therapy in patients with disseminated disease.

8.8 Treatment of Cryptococcus *Infection*

Cryptococcal pulmonary disease can be successfully treated with fluconazole monotherapy. Dosing ranges from 200 to 800 mg per day. Duration of therapy is varied based on clinical and serologic response. In the presence of CNS disease, immunocompromised patients should be treated with a combination of antifungal medications, amphotericin B 0.7–1.0 (mg/kg)/day, and oral flucytosine 100 (mg/kg)/day for 2 weeks followed by fluconazole 400–800 mg/day. Lipid-based amphotericin B preparations may be utilized (e.g., Ambisome 7.5–10 mg/kg/day).

It is important to note that the above data is based on studies conducted in immuno-compromised patients, specifically patients with HIV/AIDS. However, non HIV/AIDS currently follow a similar treatment paradigm but may require a longer duration of treatment.

8.9 Treatment of Blastomycosis

Multiple treatment options exist for the management of blastomycosis. Antifungal options include amphotericin B preparations, itraconazole, and fluconazole. Although case reports have indicated the effectiveness of each of the above stated options, there is no data from randomized clinical trials to differentiate effectiveness of the various agents. For patients with disseminated disease, clinicians often opt for the polyenes followed by the triazoles for consolidative treatment. In contrast, cutaneous blastomycosis is primarily treated with oral triazoles.

Key Points

- There are several new treatment options for the management of invasive fungal infections. Clinicians must choose the medication which best suits the patient, the disease state, and the spectrum of drug activity.
- There has been a significant change in the epidemiology of invasive candidiasis; no longer is *C. albicans* the primary species associated with invasive disease.
- *Candida* speciation and drug susceptibility testing are becoming standard of care. Non-*albicans* species demonstrate variable resistance to both azole and polyene antifungals.
- In the management of invasive aspergillosis, combination therapy offers an interesting treatment option; however, its primary utilization needs to be validated by a randomized clinical trial.

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Part II
Evidence-Based Management of Infectious Diseases

Upper Respiratory Infections and Acute Bronchitis

Arch G. Mainous III and William J. Hueston

1 Introduction

Upper respiratory infections include the following: 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 commonly seen in outpatient settings and are widely treated with antibiotics. In fact, these conditions 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 conditions.

2 Uncomplicated Upper Respiratory Infection/Common Cold

2.1 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. While a low-grade fever in some cases is present, in adults, temperature elevation is rare. 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 week, with most patients improving by the 10th day; however, lingering symptoms may last up to 2 weeks.

A.G. Mainous III (✉)
Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: mainouag@musc.edu

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2.2 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, 4]. Adults have two to four URIs annually, and children in day care have as many as six or seven [5, 6].

The significant costs of URIs can be conceptualized as both direct and indirect costs. The direct costs of URIs include the costs associated with the substantial number of office visits. URIs account for more than 36 million physician office visits a year [7]. 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 [8]. The total economic impact of non-influenza-related URIs has been estimated to approach $40 billion annually (direct costs, $17 billion per year; and indirect costs, $22.5 billion per year) in the United States [9].

Indirect costs for URIs include productivity losses related to lost workdays for adults who are sick as well as adults who have to deal with 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 [10, 11], a large proportion of children are not immunized on schedule due to visits for URIs [12]. 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 [13] and hand-to-hand contact [14]. 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 as compared to crowded poorly ventilated rooms regardless of temperature [15].

2.3 Etiology

Viruses have been shown to be the major pathogens in URIs [16]. One study established viral etiology in 69% of URIs [17]. Rhinoviruses were found in 52% of the patients by viral culture or 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 beta-hemolytic group A *Streptococcus*. In terms of bacterial pathogens, infections without evidence of a viral infection occurred in only 0.05% of the cases.

2.4 Treatment

A variety of studies in the 1990s showed a high rate of prescribing antibiotics for URIs [18, 19]. More recent data have indicated a drop in the prescribing of antibiotics; however, the use of antibiotics is still far from optimal [20]. Controlled trials of antimicrobial treatment of URIs have consistently demonstrated no benefit [21, 22]. In eight trials of antimicrobial treatment of URIs, six found no difference between the groups either in terms of improvement or in terms of 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 [23]. Another found a decrease in rhinorrhea at day 5 but no difference between the groups at day 10 [24]. Similarly, an additional trial attempted to isolate "bacterial colds" for which antibiotics might be effective treatments [25]. Although there was some indication of patient improvement at day 5, the differences were gone by day 10. It is important to remember that the normal presentation of a URI is a week to 10 days.

Few successful treatments have been identified. Vitamin C, zinc gluconate, and Echinacea have all shown mixed results [26, 27]. Antihistamines, with a few exceptions, have not been shown to be effective treatments [28]. The most effective symptomatic treatments are over-the-counter decongestants [9].

3 Acute Sinusitis

3.1 Clinical Description

Acute sinusitis has considerable overlap with URIs in its constellation of signs and symptoms. One half to two thirds of patients with sinus symptoms seen in primary care are unlikely to have sinusitis [29]. In 300 patients who presented with a URI, 19% had radiographic evidence of maxillary sinusitis but had no symptoms of sinus infection [25]. 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 sinus inflammation with no clinical signs of sinusitis and with complete resolution following their viral illness [30].

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, exhibiting symptoms such as maxillary toothache, purulent nasal discharge, poor response to decongestants, and a history of discolored nasal discharge [31, 32]. Other authors have stressed that the symptoms need to persist longer than 1 week to distinguish sinusitis from a URI [33]. It should be pointed out that the commonly used sign of facial pain or swelling has low sensitivity for acute sinusitis [32].

3.2 Epidemiology

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

In children seen in a large health system, sinusitis is frequently found as a comorbidity with otitis media. Nearly half of all children with sinusitis also had otitis media [34]. Children are also more likely to have posterior ethmoidal and sphenoid inflammation, while adults have mainly maxillary and anterior ethmoidal sinusitis [35]. Some medical conditions may increase the risk for sinusitis; these include cystic fibrosis, asthma, immunosuppression, and allergic rhinitis [36]. Cigarette smoking may also increase the risk of bacterial sinusitis during a cold because of reduced mucociliary clearance.

3.3 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 above, 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 [37]. When sinusitis is confirmed by a CT scan, response rates to antibiotics are improved [38].

Cultures of material obtained from patients with sinusitis show that the most prevalent organisms are *Strep. pneumoniae* and, especially in smokers, *H. influenzae.* These two organisms are present in 70% of cases of bacterial acute sinusitis [39]. When antibiotics are used for the treatment of bacterial sinusitis, the 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 [39].

3.4 Treatment

Antibiotics are commonly prescribed for adult patients who present with complaints that are 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 [37, 38, 40]. Two of these trials showed no beneficial effect of antibiotics [37, 40]; the third trial, however, demonstrated a significant effect of penicillin and amoxicillin [38]. The trial showing an effect used more stringent enrollment criteria than the other two; the criteria in the trial 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 short-duration treatment (e.g., 3 days) is as effective as longer treatment [41]. Further, narrow-spectrum agents seem as effective as broad-spectrum agents [42].

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

4 Acute Otitis Media

4.1 Clinical Description

The evaluation and management of otitis media has been subject to a wide variance in approaches. 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 [43]. In this study, antibiotics were used over a wide range (31–98%) of episodes of otitis media with similar variation in the types of antibiotics used and duration of therapy. To help bring some consensus to the process, the American Academy of Pediatrics issued a guideline for the evaluation and treatment of otitis media in 2004 [44]. While the guideline suffers from a lack of definitive evidence in several areas of care, the recommendations are an effective tool for bringing some clarity to an issue that has suffered from a wide variation in management strategies.

The AAP guideline recommends that the diagnosis of otitis media requires three essential components: an acute onset of illness, presence of a middle ear effusion, and signs and symptoms of middle ear inflammation. Middle ear effusion is evident in children with bulging of the tympanic membrane, reduced or absent mobility of the membrane with pneumatic otoscopy, an air–fluid level behind the membrane, and pain in the effected side. Inflammatory signs noted in the report include erythema of the tympanic membrane along with pain on that side. In considering all these factors, the combination of reduced mobility, erythema, and a bulging tympanic membrane is the best predictor of otitis media.

The most essential step in managing otitis media is assuring that the diagnosis is correct. Otitis media may be overdiagnosed, especially in younger children, which complicates the evaluation of treatment effectiveness. Studies show that a physician's certainty about the diagnosis of otitis media is 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 [43]. This increased to 66% in those between 1 year and 30 months of age and up to 73% in those over 30 months of age.

4.2 Epidemiology

Historically, acute otitis media has been one of the most common pediatric conditions seen in primary care. However, since the introduction of vaccines

against common respiratory pathogens, there is evidence that the frequency of this problem has decreased considerably. In the Netherlands, visits to general practitioners for otitis media with effusion in children under the age of 2 fell by 66% between 1995 and 2003 [45]. A similar decrease in visits for acute otitis in children has been reported in a large health system in the United States [46], with a smaller reduction in visits noted in the emergency department setting [47]. The introduction of *H. influenzae B* vaccine in the 1980s, followed by universal childhood immunization with conjugated *Strep. pneumoniae,* may be responsible for the reduction in otitis media cases encountered.

Since otitis media is a complication of an upper respiratory infection, 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 months of age [48]. Otitis media occurs with varying frequency in children. In a large population study, it was found that during the first 3 years of life about a third of children never had otitis media and another third had one or two episodes, while 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.

4.3 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 *Strep. pneumonia* is the most common bacterial cause of otitis media and is found in about 40% of effusions. *H. influenzae* accounts for approximately 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 above, is one such mechanism. Other causes include enlargement of the adenoids and posterior pharyngeal tumors.

4.4 Treatment

Treatment recommendations from the AAP/AAFP guidelines for the management of acute otitis media suggest that observation rather the initial use of antibiotics is appropriate depending on the child's overall health, age, severity of illness, and likelihood that they can follow-up if necessary. For healthy children over the age of 2, antibiotics are recommended only if the child is severely ill; if the child is mildly ill or if the diagnosis is uncertain, then observation is acceptable. For children younger than this, antibiotics are recommended for a certain diagnosis of otitis media and for those under age 6 months where the diagnosis is uncertain. Antibiotics are not recommended for use in healthy children between 6 months and 2 years who have an uncertain diagnosis (AAP Subcommittee). If patients who are observed fail to improve in 48–72 h, then antibiotic therapy is recommended.

Based on the AAP/AAFP guidelines, routine observation or "wait and see protocol (WASP)" as an alternative to universal antibiotic use has been evaluated in emergency room setting. A randomized trial of the WASP approach compared with routine antibiotics showed that antibiotic use was reduced from 62 to 13% with no differences in prolonged fever, ear pain, or unscheduled subsequent visit for the ear infection [49]. Despite evidence that the WASP or observation period is effective, primary care physicians have been slow to adopt this in practice [50].

When antibiotics are selected for the management of acute suppurative otitis media, selection of an agent should provide coverage for the two most common organisms, the AAP/AAFP recommends initial treatment with amoxicillin at a dose of 80–90 mg/kg per day. Second, the duration of antibiotic treatment is unclear. In a meta-analysis of trials that compared short-duration antibiotic therapy with the traditional 10 day course, no benefit was found of using longer courses of treatment; however, methodologic problems may complicate the interpretation of these results [51]. In their guidelines, the AAP/AAFP recommends that a 5–7 day 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 be equally beneficial to longer courses of amoxicillin [52], cefaclor [53], or trimethoprim–sulfamethoxazole [54] for the treatment of acute suppurative otitis media. Where antibiotic resistance to *S. pneumonia* is high or where patient compliance is an issue, ceftriaxone may be a viable alternative. In addition, some studies have evaluated the use of a single dose of azithromycin (30 mg/kg) for treatment of uncomplicated otitis media. In a review of these studies, the overall success rate was 82% [55]. Macrolide resistance to *S. pneumoniae* was the largest impediment to success. Based on this, it was suggested that

single-dose azithromycin may be an alternative in areas with resistance to *S. pneumoniae* is uncommon.

The primary concern in the treatment of otitis media is a primary treatment failure (i.e., persistent illness or an early recurrence of disease following initial therapy of a new otitis episode) [56]. A meta-analysis of 33 randomized trials supports initial antibiotic use demonstrated no significant differences in failure rates when comparing "standard" or first-line (penicillin, amox/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 [57, 58], with children younger than 2 years of age having treatment failures in 26–37.5% of cases. For older children, treatment failures occur in 2–19% of episodes [57, 58].

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 TMP–SMX [59].

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 SMX–TMP adds 16% to the overall cost of the episode [56]. 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 *S. 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.

5 Tonsillitis/Pharyngitis

5.1 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 15–30% are secondary to infection with group A beta-hemolytic streptococcus. The primary role of the physician is to differentiate streptococcal pharyngitis from viral illnesses.

Since 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 is one of the most common diagnoses for physician office

visits. Estimates from 2005 suggest that more than 11 million visits in the United States each year are for pharyngitis [7]. Frequently antibiotics are prescribed for these conditions without evidence of a bacterial etiology.

5.2 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 year old) is uncommon, the peak occurrence for strep throat is between 5 and 15 years of age with diminished risk over the age of 20.

5.3 Etiology

The most common causes of pharyngitis are respiratory viruses. Adenovirus and the rhinoviruses account for about 80% of cases of sore throat in children that are seen by physician [60, 61]. Coxackievirus, herpesvirus, and Epstein–Barr virus can cause tonsillitis but are less common that adenovirus [62]. Adenovirus, coxackievirus, and Epstein–Barr virus can cause exudative pharyngitis that can mimic the appearance of streptococcal infection. While exudative tonsillitis is thought to be a hallmark of group A streptococcal infection, this sign is actually present more often from adenovirus than streptococcus. It is important to identify group A streptococcal infections because trials of antibiotics in undifferentiated sore throat populations show little benefit [63].

Group A beta-hemolytic streptococcus can cause an acute tonsillopharyngitis and may colonize the oropharynx without symptoms. The asymptomatic carrier rate of group A strep ranges from about 10 to 30% of healthy children, a rate that nearly matches the true infection rate [64, 65]. This means that in testing for group A streptococcus, positive tests are just as likely to occur from carriers of group A strep 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 reduce complications [66].

The reasons for antibiotic treatment of beta-hemolytic group A streptococcal pharyngitis are to alleviate symptoms, reduce the spread of disease, and reduce the risk of suppurative and nonsuppurative complications. Although some authors have suggested that antibiotics are not justified to reduce the risk of rheumatic fever, a complication of beta-hemolytic group A streptococcal pharyngitis, the American Heart Association in 2009 still recommends antibiotic treatment [67, 68].

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 [69–71]. A clinical prediction rule for presence of strep throat that has some utility uses the presence of tonsillar exudate, pharyngeal exudate, or exposure to strep throat infection and the absence of tender anterior cervical nodes, tonsillar enlargement, or exudate. No individual element of history-taking or physical examination is accurate enough by itself to rule in or rule out strep throat [72]. Another dilemma in identifying group A strep 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 strep. The rapid tests have a high degree of specificity, but their sensitivity in clinical practice can be unacceptably low. 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 seroconversion of ASO titers is used as the gold standard for infection, rapid tests perform very well [69]. It is likely that rapid tests miss patients who have a small number of organisms and who are likely to be colonized instead of infected. Thus, rapid testing may be more specific in identifying patients with actual strep-related disease than cultures, which also identify those who are likely to be carriers. This comparison suggests that follow-up throat cultures are not necessary and may actually confuse treatment decisions. Rapid strep testing without culture also has been shown to be the most cost-effective approach to managing acute pharyngitis [73].

As indicated above, 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 strep pharyngitis [74], patients who received placebo had the same speed of symptom resolution as those treated with active antibiotics.

5.4 Treatment

5.4.1 Group A Beta-Hemolytic Streptococcal Tonsillopharyngitis

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 [75]. However, formal decision analyses suggest that in cases of moderate probability of strep throat (40–85%) with symptom duration of 2 days or less, rapid strep testing and treatment is beneficial [76].

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

as well as erythromycin resistance has led to investigations of other drugs for management of strep throat. Since 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 since 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 [77, 78]. However, single-dose therapy with amoxicillin at 40 mg/kg/day for 10 days appears to be very successful resulting in excellent clinical responses and low rates (5–10%) of posttreatment carrier rates [77, 78]. Treatment with other agents such as azithromycin and clarithromycin produces no better results than amoxicillin or penicillin V [79–81]; however, these treatments amount to a much greater expense.

Attempts at "short-course" therapy have been studied with azithromycin [82]. Both short-course treatment with azithromycin and 10 days of cefaclor have exactly the same clinical cure rates (86%) by day 3 of therapy. However, patients treated with cefaclor were less likely to become recolonized with group A strep over the next 45 days than those treated with the short course of azithromycin (20% vs. 55%). Since the significance of rapid recolonization is still unclear, short-course therapy with azithromycin or other antibiotics still requires additional investigation.

5.4.2 Group A Streptococcal Carriers

While the carrier rate does not require treatment [66], some clinicians attempt to eradicate those colonized by group A strep 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 [83]. There have been no studies performed more recently that have explored whether this regimen remains effective with increased group A strep resistance to penicillin.

5.4.3 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 [69], 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 which would allow for targeted treatment and studies can demonstrate that treatment reduces symptoms and complications, indiscriminate antibiotic therapy for non-group A strep pharyngitis should be avoided.

6 Acute Bronchitis

6.1 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 weeks and 25% had a cough for more than 4 weeks [84].

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 since they have different treatments.

Both acute bronchitis and pneumonia can present with fever, constitutional symptoms, and a productive cough. While 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, since 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.

6.2 Epidemiology

Acute bronchitis in the otherwise healthy adult is one of the most common medical problems encountered in primary care [4, 7]. The prevalence of acute bronchitis peaks in the winter and is much less common in the summer.

6.3 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 [85]. Nonviral pathogens including *Mycoplasma pneumoniae* and *C. pneumoniae* (TWAR) have also been identified as causes [86, 87].

The etiologic role of bacteria like *H. influenzae* and *S. pneumoniae* in acute bronchitis is unclear since these bacteria are common upper respiratory tract flora. Sputum cultures for acute bronchitis are therefore difficult to evaluate since it is unclear whether the sputum has been contaminated by pathogens in the nasopharynx.

6.4 Evaluation

Usually, laboratory and imaging tests are not needed in the diagnosis of acute bronchitis. However, a new test under consideration might be helpful in differentiating viral acute bronchitis from more serious bacterial infections such as pneumonia. By measuring procalcitonin, a precursor to the hormone calcitonin, Christ-Crain and colleagues have been able to distinguish patients at high risk for bacterial infections (those with higher procalcitonin levels) from those with low risk for bacterial infection. Evaluation of this method in the emergency department has led to reductions in antibiotic prescribing without any differences in clinical outcomes for patients presenting with acute cough syndromes [88]. While a point-of-care version of the test for procalcitonin has been developed that can be done quickly in a physician's office, the test is still expensive and has not been evaluated outside the emergency department.

6.5 Treatment

Antibiotic treatment for acute bronchitis is quite common with evidence indicating that 60–75% of adults visiting a doctor for acute bronchitis receiving an antibiotic [19, 89]. Clinical trials of the effectiveness of antibiotics in treating acute bronchitis have had mixed results. One reason for the lack of consensus is that in each of the nine trials, different antibiotics were used as well as different outcomes. In an effort to quantitatively review the data, two different meta-analyses were recently conducted [90, 91]. In the Fahey et al., meta-analysis resolution of cough was not affected by antibiotic treatment and neither was clinical improvement at re-examination. 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 [92, 93]. 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 [94]. Since 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 are account for a large proportion of total outpatient healthcare 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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Pneumonia

Hien H. Nguyen

1 Introduction

The management of pneumonia remains one of the most dynamic areas of medicine. Due to its high prevalence and mortality rate, changing antimicrobial resistance patterns, and evolving treatment algorithms, pneumonia deservedly takes its place as Sir William Osler noted over a century ago as the "Captain of the Men of Death" [1]. While the diagnosis and management of pneumonia will continue to evolve as more data refine our knowledge, a number of regulatory bodies such as the Center for Medicare and Medicaid Services and the Joint Commission on Accreditation of Healthcare Organizations have chosen pneumonia as an indicator for quality care. Current knowledge of evidence-based practice will be important not only for successful patient outcomes but also as a measured indicator of the level of quality provided by the clinician and healthcare organization.

Pneumonia can be caused by a wide array of bacterial, viral, and fungal etiologies, and it can affect any age group. This chapter will focus on the treatment of adults with bacterial community-acquired (CAP) and healthcare-associated pneumonia (HCAP).

2 Community-Acquired Pneumonia (CAP)

2.1 Epidemiology

In the United States, pneumonia, along with influenza, is the eighth leading cause of death with approximately 60,000 deaths annually [2]. However, the overall burden of this disease is not clearly captured by this lone statistic. There are approximately

H.H. Nguyen (✉)
Division of Infectious Diseases, Division of Pulmonary Critical Care Medicine, Department of Internal Medicine, Davis Health System, University of California, Sacramento, CA, USA
e-mail: hien.nguyen@ucdmc@ucdavis.edu

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4 million cases of pneumonia each year with a quarter of cases resulting in hospitalization and totaling more than $9 billion a year in costs [3]. In the population over the age of 65, it is estimated that over 900,000 cases of pneumonia occur annually and that 1 of every 20 persons over the age of 85 will have a new episode of pneumonia each year [4].

Despite its prevalence and the ample amounts of research conducted on this condition, outcomes related to pneumonia have not improved since the development of penicillin [5]. In fact, adjusted and unadjusted mortality rates may have increased. This is due, in part, to the increased proportion of the population over age 65 with underlying medical conditions and to other host factors that may affect mortality. The recognition that the status of the host plays a significant role in the outcome of this infection has influenced the management of CAP significantly. This has, in part, led to the development of several prognostic scores based on host factors associated with mortality (see Section 2.4 below).

2.2 Etiology

A good understanding of the pathogens that may cause pneumonia forms the foundation for understanding the guidelines for diagnostic tests and empiric antimicrobial use (Fig. 1) [6]. The most common bacteria causing CAP can be divided into two general categories: typical and atypical. Typical organisms include *Streptococcus pneumophila*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. Atypical organisms include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*,

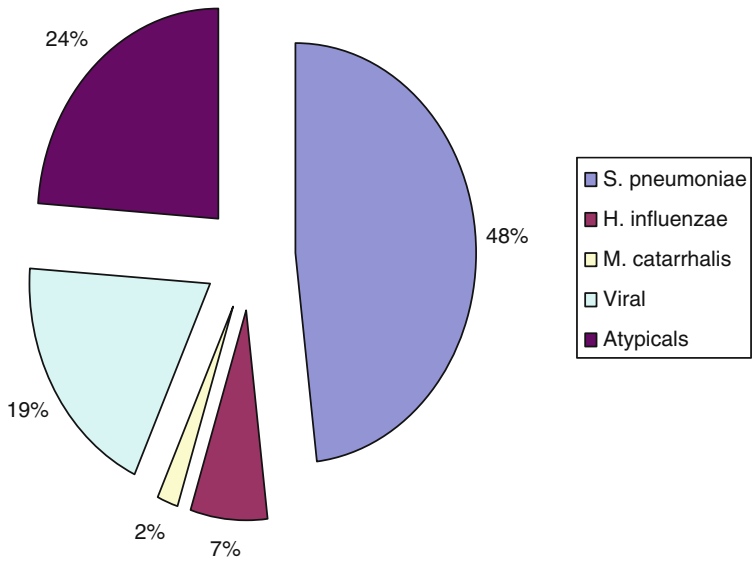

Fig. 1 The common etiologies of community-acquired pneumonia

Table 1 Common etiologies of severe community-acquired pneumonia requiring admission to the intensive care unit

Patient type	Etiology
Outpatient	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* Respiratory viruses
Inpatient (non-ICU)	Outpatient etiologies, plus: *Legionella* species Aspiration
Inpatient (ICU)	*S. pneumoniae* *S. aureus* *Legionella* species Gram-negative bacilli *H. influenzae*

and *Legionella pneumoniae*. Generally, atypical organisms are more difficult to diagnose by gram stain or standard bacterial culture (although *S. pneumoniae* can also be difficult to culture), and, from a practical standpoint, typical and atypical organisms entail treatment with different classes of antibiotics. Typical organisms often respond to beta-lactam antibiotics, while atypical organisms generally require use of macrolide or fluoroquinolone antibiotics.

The severity of illness, although not reliable, may also be an indicator of the type of bacteria causing illness (Table 1) [7]. With the exception of *Legionella spp.*, atypical organisms generally cause less severe disease while infections with typical organisms are more often responsible for patients hospitalized for pneumonia. Severe infections resulting in admission to an intensive care unit may also broaden the potential list of bacteria to consider, including *Staphylococcus aureus* (especially during an influenza outbreak). In immunocompromised patients, specific defects in immunity predispose to infection with a broad array of additional organisms.

2.3 Diagnosis

Prompt and accurate diagnosis of pneumonia is extremely important. Typically, without proper treatment, the outcome of infection is evident 6–10 days after the start of illness, with a case-fatality rate of approximately 40%. However, with treatment, the rate is about 5%. The diagnosis of pneumonia can be difficult to make due to the frequency of acute respiratory symptoms as a reason for visiting a physician in the office. In fact, respiratory symptoms accounted for approximately 3% (approximately 27 million visits) of all office visits in 2004, with only a small proportion due to pneumonia [8]. While appropriate treatment of pneumonia is important, overutilization of antimicrobials for acute respiratory symptoms (which are often due to viral infections) can lead to increased antibiotic resistance among common respiratory pathogens. Therefore, making the appropriate diagnosis is not only important for good patient care but also to avoid unnecessary use of antimicrobials.

The diagnosis is based on clinical signs and symptoms as well as laboratory and imaging tests. Typical presentations of pneumonia start with a sudden single, shaking chill followed by sustained fever and a productive cough. However, clinical signs and symptoms of pneumonia can vary and are often subtle, particularly in the elderly. In fact, early on, at the onset of symptoms, there may be only fever, pleuritic chest pain, and a nonproductive cough. Generally, 12–24 h later, with intravenous fluid hydration, a clear infiltrate on chest radiograph and physical exam findings of consolidation are present. Cough tends to be the most common respiratory symptom and is present in over 80% of cases. Fever, while common in the young, can be absent in the elderly or seriously ill. Other respiratory symptoms may include dyspnea and hemoptysis. While clinical signs and symptoms may appear obvious, it is typically the nonrespiratory symptoms that are more concerning because they may mask or delay the diagnosis. Marked confusion or altered mentation may be the most prominent sign of pneumonia in the elderly and is more common in *Legionella* sp. and psittacosis pneumonias. Acute abdominal pain may be the most prominent sign in lower lobe pneumonias and *Legionella* sp. infections.

The physical examination may show diminished breath sounds, rales, wheezes, increased tactile fremitus, dullness to percussion, egophony, or whispering pectoriloquy (transmission of whispered or spoken voice). These signs all relate to the replacement of air in the lungs with exudate. Unfortunately, the sensitivity of these physical exam findings is poor, ranging from 47 to 69% in one study [9], and a diagnosis should also include laboratory and imaging studies, with or without confirmatory microbiologic studies.

2.3.1 Diagnostic Tests

Diagnostic testing should usually include a leukocyte count and a chest radiograph. Neutrophilia or a left shift usually indicates a bacterial infection, although in immunocompromised or elderly patients, neutrophilia may not be present. Chest radiographs are helpful not only in confirming the replacement of air in the lungs with exudate or evidence of inflammation but also in revealing other evidence of a pulmonary process such as a parapneumonic effusion, abscess, or cavity. Cavitary lung findings may also lead to consideration of less common etiologic bacteria such as *S. aureus*, *Klebsiella* spp., other gram-negative bacteria, or a mixed aerobic/anaerobic infection. Additionally, patients should be screened with pulse oximetry, which may be helpful in suggesting the presence of a pulmonary process in patients without obvious signs of pneumonia.

Patients with CAP should have cultures obtained to confirm a specific pathogen if they are critically ill or when circumstances occur that may alter appropriate choices of empiric antimicrobial management. While a routine diagnostic evaluation with blood or sputum cultures is discouraged in most patients because of the low yield and possible delays in therapy secondary to obtaining these cultures before antimicrobial initiation, these cultures may be useful for individual patients, especially those who are seriously ill or have underlying immunodeficiencies, and give valuable epidemiologic information on pathogen frequency

and antimicrobial resistance patterns. Treatment should never be delayed for these tests.

Additionally, urinary antigen testing (UAT) may be helpful in making a microbiologic diagnosis for *S. pneumoniae* and *L. pneumoniae*, serotype 1. The advantages of *S. pneumoniae* UAT are its rapidity (approximately 15 min) and the ability to detect this pathogen after antimicrobial therapy has been started. In this scenario, a microbiologic etiology can be confirmed and antimicrobial therapy may potentially be narrowed. UAT for *Legionella* is useful because of the difficulty in culturing this organism in standard sputum cultures. The clinical indication for use of the *Legionella* test is in determining whether an environmental exposure caused an infection. Identification of *Legionella* may prevent exposure of other susceptible patients. Recommendations for use of additional microbiologic tests are listed in Table 2 [7].

Table 2 Recommendations for additional diagnostic microbiology tests for community-acquired pneumonia

Additional diagnostic testing	Clinical indication
Legionella urinary antigen	ICU admission
	Failure of outpatient antibiotic therapy
	Active alcohol abuse
	Recent travel (within past 2 weeks)
	Pleural effusion
Pneumococcal urinary antigen	Above indications
	Leukopenia
	Chronic severe liver disease
	Asplenia (anatomic or functional)
Endotracheal aspirate	ICU admission
Fungal and tuberculosis cultures	Cavitary infiltrates
Thoracentesis and pleural fluid cultures	Pleural effusion

2.4 Management and Treatment

The management of CAP requires three major components: determination of the need for hospitalization and intensive care unit admission, timing and choice of empiric therapy, and other supportive measures that reflect high-quality care.

Determination of the site of care is based on the initial assessment of pneumonia severity. Because this decision impacts overall management approaches, it is a crucial step in CAP management. The advantages of treating patients at low risk of death in the outpatient setting include resuming normal activity sooner, lower risk of thromboembolic events and other nosocomial complications, lower cost, and greater patient satisfaction. However, physicians, in the past, have tended to overestimate clinical severity [10], which has resulted in the development of a

number of objective scoring systems to help assess severity and need for hospitalization. It should be noted that these scoring systems were never meant to replace clinical judgment and should only be used as a tool to augment the decision-making process.

The pneumonia severity index (PSI) was based on derivation and validation cohorts totaling more than 50,000 patients with CAP [11]. The PSI uses host factors and initial clinical signs and symptoms to stratify patients into five mortality risk classes (Table 3). On the basis of overall mortality in the classes, it is suggested that patients in classes 1 and 2 can be treated as outpatients and classes 4 and 5 should be admitted to the hospital. Risk class 3 should be closely observed and potentially admitted for a short hospitalization. This prognostic model method of risk stratification is based on very low mortality rates of 0.1–0.4%, 0.6–0.7%, and 0.9–2.8% in classes 1–3, respectively.

Table 3 Pneumonia severity index scoring system

PSI risk class	Mortality rate (%)
Class I	0.1
Class II (score $\leq$ 70)	0.6
Class III (score 71–90)	0.9
Class IV (score 91–130)	9.3
Class V (score >130)	27

Another scoring system, based on severity of illness, was developed by the British Thoracic Society and dubbed the CURB-65 score (Table 4). The score is based on five criteria: confusion (based on a specific test for disorientation), blood urea nitrogen level (>20 mg/dL), respiratory rate ($\geq$30 breaths per minute), blood pressure (systolic <90 mmHg or diastolic $\leq$60 mmHg), and age $\geq$65 years. The score gives 1 point for fulfilling each criteria. Scores of 0–1 can be treated as outpatients with 30 day mortality rates of 0.7 and 2.1%. Scores of 2 should be admitted and scores of 3 or greater generally required ICU care [12]. A simplified version, which does not require measuring a BUN level, may be useful in the primary care practitioner's office [13]. While both scores offer assistance in determining the need

Table 4 CURB-65 scoring system

CURB – 65 criteria	Definition
C = confusion	New disorientation in person, place, or time
U = urea	BUN > 20 mg/dL
R = respiratory rate	RR $\geq$ 30/min
B = blood pressure	Systolic BP < 90 or diastolic BP $\leq$ 60 mm Hg
65 = age	Age $\geq$ 65

for admission, the CURB-65 score may be more direct in assessing the need for hospitalization.

The time to first antibiotic dose for empiric therapy has been incorporated into the Joint Commission and the Center for Medicare and Medicaid Services' core measures, which may reflect the overall quality of patient care for CAP. While it seems reasonable that the first dose of antibiotics should be given as soon as possible after the diagnosis is considered likely, there continues to be some controversy over the resultant circumstances of imposing a deadline as a measure of quality for the first dose of antibiotics. The time to the first dose of antibiotics that CMS and the Joint Commission consider a quality measure for pneumonia therapy is 4 h after presentation. An initial study suggested that 30 day mortality increased when antibiotics were given 8 h after presentation [14]; however, a subsequent study, which limited the cohort to patients with criteria of a suspected diagnosis of pneumonia at admission, radiographic evidence of pneumonia at admission, and a principal diagnosis of pneumonia suggests that delays up to 4 h may increase mortality [15]. It should also be noted that these data were collected from patients aged 65 years or above.

The controversy over an imposed deadline as a measure of quality is grounded in the observation that pneumonia can be difficult to diagnose in the elderly, especially when presenting with altered mental status. As a result, many feel that the 4 h rule is not a good measure of quality [16]. Additionally the treatment of patients in the emergency room can be adversely affected when health systems try to meet quality indicators either by giving everyone with respiratory symptoms a dose of antibiotics to ensure they meet the deadline or by triaging potentially less ill patients with respiratory complaints ahead of more ill patients in order to quickly assess for pneumonia. The IDSA/ATS guidelines recommend that the first dose is given in the emergency department, without reliance on a time deadline [7].

Empiric treatment of CAP is based on the treatment of the most common causes of pneumonia as discussed above, and the choice of therapy is also considered an indicator of quality (Table 5) [7].

While the selection of an appropriate antimicrobial agent is an important step in the management of CAP, the decision on whether or not to prescribe antimicrobials is equally important. With growing bacterial resistance rates, it is important that primary care practitioners continue to judiciously prescribe antimicrobials when indicated. Of note, bronchitis and sinusitis are generally secondary to viral pathogens and do not require the use of antibacterials. The amount of use of antibiotics in hospitals has been tracked and directly correlated with increased bacterial resistance rates. Similarly, when the community use of antibiotics by primary care practitioners has been tracked, the amount of antibiotic use in the community impacts rates of resistance in hospitals as well [17]. These points reinforce the notion that antimicrobials must be used judiciously in all healthcare settings.

Table 5 Recommendations for empiric treatment of community-acquired pneumonia

Patient status	Treatment
Outpatient (previously healthy without history of antimicrobials in the last 3 months)	Macrolide or Doxycycline
Outpatient (comorbidities such as chronic heart, lung, liver or renal disease, diabetes, alcoholism, malignancy, asplenia, immunosuppressed, or history of antimicrobials in the last 3 months)	Respiratory fluoroquinolone or Beta lactam plus macrolide
Inpatient (non-ICU)	Respiratory fluoroquinolone or Beta lactam plus macrolide
Inpatient (ICU)	Beta lactam plus Either azithromycin or respiratory fluoroquinolone
Inpatient (with concern of *Pseudomonas*)	Antipneumococcal, antipseudomonal beta lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) plus ciprofloxacin or levofloxacin or Above beta lactam plus either aminoglycoside or azithromycin or Above beta lactam plus azithromycin and aminoglycoside
Inpatient (with concern of methicillin-resistant *Staphylococcus aureus*)	Add vancomycin or linezolid to regimen

3 Hospital-Acquired Pneumonia (HAP) and Healthcare-Associated Pneumonia (HCAP)

3.1 Epidemiology

By definition, hospital-acquired pneumonia (HAP) is pneumonia that was not present on admission and was diagnosed at least 48 h after hospitalization. While the signs and symptoms of CAP and HAP are similar, the underlying reason for making a distinction between CAP and HAP lies in the higher risk for multidrug-resistant infections in HAP, which dramatically changes the choice of empiric antibiotics.

Additionally, with a growing number of chronically ill elderly patients, the category of healthcare-associated infections has also emerged. Healthcare-associated infections are defined as infections that arise from contact with a healthcare setting, most commonly skilled nursing facilities, home health settings, dialysis clinics,

and recent hospitalizations (within 90 days). While healthcare-associated infections have in the past been categorized as a "community" infection due to the onset occurring outside of the hospital, there is growing recognition that the types of organisms causing these infections are similar to those that patients acquire in a hospital setting. Since the treatment and management of healthcare-associated pneumonia (HCAP) is similar to HAP, treatment recommendations are generally similar. Ventilator-associated pneumonia (VAP) is considered as a form of HAP in this discussion.

The management and prevention of HAP has received special attention from health plans, which look at nosocomial infections as potentially preventable conditions. Thus, payors like the Centers of Medicare and Medicaid Services are considering denial of payments for prolonged hospital stays due to these hospital-acquired complications. Additionally, many states are considering or have implemented public reporting of these infections with the hope that it will stir efforts to prevent these infections. While HAP is not among the first set of nosocomial infections to undergo these kinds of regulatory pressures to improve patient outcomes, regulations related to HAP are expected.

HAP is second only to urinary tract infections as the most common nosocomial infection and is associated with the highest morbidity and mortality [18]. The development of this infection increases hospital stays on average 7–9 days and is associated with a cost of over $40,000 per patient. Due to its impact on patient outcomes, clinicians tend to overprescribe antibiotics for suspected but unproven VAP. Additionally, by accounting for more than half of the antibacterials prescribed in the ICU, HAP is likely the single most important infection responsible for overutilization of antibacterials in hospitals.

3.2 Etiology and Prevention

Critically ill patients are colonized by bacteria found in the intensive care unit (ICU). The longer patients spend in the ICU, the higher the likelihood of colonization. These colonizing bacteria subsequently are the microorganisms responsible for HAP (Table 6) [18]. Healthcare workers can act as transient carriers, transferring and spreading bacteria in the ICU from one patient to the next. Hand hygiene may prevent the spread and colonization of multidrug-resistant bacteria within the ICU. With regard to nosocomial pneumonia, the oral pharynx becomes colonized with bacteria within the ICU, and it is thought that microaspiration of secretions of the mouth and GI tract causes VAP. Ironically, when older ventilation systems, like the iron lung, were used, less ventilator-associated pneumonia was seen than with our modern version of mechanical ventilation. The plastic tube that is inserted into the airways essentially bypasses the body's normal defense mechanisms that prevent infection of the lungs.

Prevention of HAP can occur with three different steps: First, methods can be employed to prevent use of mechanical ventilation. The use of noninvasive ventilation has been shown to prevent VAP and other nosocomial infections. Essentially,

Table 6 Common etiologies of hospital-acquired pneumonia

Patient status	Pathogens
Hospital acquired	*S. pneumoniae*
Early onset (within 7 days of admission)	*H. influenzae*
Without previous antimicrobial exposure	*S. aureus*
	Susceptible enteric gram-negative bacilli (*E. coli, K. pneumoniae, Enterobacter* species, *Proteus* species, *Serratia marcescens*)
Hospital acquired	Pathogens above, plus:
Late onset	*P. aeruginosa*
Previous antimicrobial exposure	*K. pneumoniae* (extended-spectrum beta lactamase)
	Acinetobacter species
	Methicillin-resistant *S. aureus*
	Legionella pneumophila

placement of an endotracheal tube can be avoided and the associated infections can be prevented. Analogously, the sooner the patient can be extubated or weaned from the ventilator, the sooner normal defense mechanisms can prevent infection. Protocols in the ICU for ventilator weaning may be effective for aggressively encouraging extubation. Daily breaks in sedation are recommended to assess readiness for extubation. Second, we can employ methods to prevent the colonization of the oropharynx with drug-resistant bacteria. The use of hand hygiene helps prevent the colonization with multidrug-resistant bacteria. In addition, aggressive oral hygiene with the use of antiseptics to prevent colonization may also decrease the risk of VAP. Finally, the prevention of microaspiration may prevent VAP; with the head of the bed at an angle of 30–45°, it is more difficult for contents of the stomach and associated bacteria to be aspirated. While the effectiveness of each of these interventions alone may have only a minimal impact in an individual patient, the use of these interventions within hospital systems as a "bundle" of practices has been shown to effectively reduce rates of VAP [19].

3.3 Diagnosis

Although the general signs and symptoms of HAP are similar to CAP, the specificity of clinical and radiographic findings in critically ill patients is poor [18]. In general, the presence of a radiographic infiltrate along with fever, leukocytosis, or purulent sputum should lead to more diagnostic testing for HAP. There are no clinical parameters that will help define a microbiologic etiology and a lower respiratory tract culture such as an endotracheal aspirate, a bronchiolar lavage, or a protected specimen brush should be performed. Even in this circumstance, however, organisms isolated in culture may simply represent colonization. As a result, HAP is generally still a clinical diagnosis.

3.4 Treatment

The choice of empiric therapy for VAP may have an impact on mortality. Delays in the initiation of antimicrobials that have adequate activity against subsequently isolated bacteria may double the overall mortality rate [20]. While adequate antimicrobial therapy is the emphasized recommended course of action for critically ill patients, it is unclear if increased mortality is seen in hospitalized non-ICU patients. The major limitation to the use of broad-spectrum antimicrobials is that it may lead to overutilization of antibiotics and consequent increased bacterial resistance patterns in hospitals. Some investigators have suggested that the overuse of antimicrobials may lead to increased morbidity as well [21]. One method of helping to balance over- and underutilization of broad-spectrum empiric antimicrobials is awareness of hospital- and unit-specific antibiograms. Specifically, examining VAP-specific antibiograms will allow creation of hospital guidelines for management of VAP in situations that require less broad-spectrum antibiotics, like early-onset VAP without prior antimicrobial exposure, and broader spectrum antibiotics, like late-onset VAP with prior antimicrobial exposure [22].

Table 7 Modified clinical pulmonary infection score

Criteria	Points
Clinical pulmonary infection score day #1	
Temperature	Tm > 39°C = 2 points
	Tm = 38.5–38.9°C = 1 point
	Tm = 36–38.4°C = 0 points
	Tm < 36°C = 2 points
White blood cell count (WBC)	WBC > 11,000 = 1 point
	WBC 4–11,000 = 0 points
	WBC < 4,000 = 1 point
	Bands > 50% = add 1 point
Chest radiograph	Localized infiltrate = 2 points
	Diffuse or patchy infiltrate = 1 point
	No infiltrate = 0 points
Tracheal secretions	Purulent secretions = 2 points
	Nonpurulent secretions = 1 point
	No secretions = 0 points
Oxygenation	$PaO_2/FiO_2 \leq 240$ and no ARDS* = 2 points
	$PaO_2/FiO_2 > 240$ = 0 points
Clinical pulmonary infection score day #3 (recalculate above plus below)	
Chest radiograph progression	Progression of infiltrate = 2 points
	No change = 0 points
Culture of tracheal aspirate	Pathogenic bacteria in moderate or heavy growth = 1 point
	Pathogenic bacteria in rare or light growth = 0 points
	Gram stain matches culture of pathogenic bacteria = add 1 point

*ARDS, acute respiratory distress syndrome (defined as ratio < 200, pulmonary arterial wedge pressure < 18, acute bilateral infiltrates).

An important component of the use of broad-spectrum antimicrobials is the de-escalation of therapy. There are generally two components of de-escalation that will improve utilization of antibiotics. The first component of de-escalation is tailoring the choice of therapy based on sputum culture results. Commonly, when cultures return on treatment day 2 or 3, a less broad-spectrum choice of therapy can replace the initial regimen. Another component of therapy relates to discontinuation of antimicrobial therapy. Using a modified version of the clinical pulmonary infection score (CPIS) (Table 7), Singh and colleagues have demonstrated that low scores on day 1 and 3 of treatment represent a patient population that may have antimicrobials safely discontinued for VAP, resulting in lower ICU stay, less drug resistance, and less cost [23]. Additionally, the duration of treatment for VAP has undergone a significant decrease as well from 2 weeks duration to 1 week for typical cases [24].

One disturbing trend in the management of multidrug-resistant bacteria found in the hospital relates to the lack of new classes of antimicrobials to treat growing bacterial resistance. Given that the research and development of new antibacterial agents generally takes over 10 years before availability of the drug, we must make concerted efforts not only to prevent HAP infections but also to prevent or slow down the rates of rising bacterial resistance [25].

4 Conclusions

Pneumonia remains an infection that has a great impact on medicine and health. As a result, the use of antimicrobials for the management of pneumonia in all of its various forms remains a challenge.

Key Points

- The management of CAP continues to evolve and has become a measure of the quality of care provided by physicians and hospitals.
- Respiratory viral illnesses should not receive antibacterials as this practice would increase rates of antibiotic resistance.
- Newer diagnostic tests are now available and recommended in making an etiologic diagnosis of CAP.
- The prevention of HAP is also considered a measure of quality and attention should be devoted to the implementation of “bundles” to prevent HAP.
- The diagnosis of VAP continues to be difficult to determine, necessitating empiric use of antibacterials for management of VAP.
- For severe HAP, due to the increased risk of multidrug-resistant bacteria, broad-spectrum antibacterial therapy should be initiated while awaiting cultures.
- De-escalation of therapy is essential in preserving antibacterial efficacy against multidrug-resistant bacteria.

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Urinary Tract Infections

Dimitri M. Drekonja and James R. Johnson

1 Introduction

Urinary tract infection (UTI) is one of the most commonly diagnosed infections, in both primary care clinics and urgent care or emergency departments [1]. The costs associated with UTI stem from a combination of lost productivity, due to time spent seeking medical care, costs of diagnostic testing, costs of antimicrobial therapy, and costs associated with hospitalization, as is sometimes indicated for more serious forms of UTI such as pyelonephritis [2]. An evidenced-based approach, combined with prudent clinical judgment, can limit costs from each of these sources [3].

This chapter will focus on specific strategies that can be used when diagnosing and treating different types of UTI and will touch briefly upon the definition, presentation, and epidemiology of each of the relevant clinical entities [1, 4]. One key principle is that outside of a few narrowly defined patient groups, the diagnosis of UTI should not be pursued in asymptomatic individuals. Adherence to this single principle has the potential to significantly reduce costs by limiting diagnostic testing, antibiotic use, selection of resistant organisms, and drug-related adverse events.

2 Cystitis

2.1 Definition, Presentation, and Epidemiology

Cystitis, defined as infection or inflammation of the urinary bladder (and often accompanied by urethral inflammation), is among the most commonly diagnosed infectious diseases [1]. It is much more prevalent among females than males; this discussion will be limited to cystitis among females. Females at greatest risk for cystitis include those who are sexually active or are postmenopausal [5]. Symptoms of cystitis include dysuria, urinary frequency, suprapubic pain, and occasionally

D.M. Drekonja (✉)
Minneapolis Veterans Affairs Medical Center, Department of Medicine, University of Minnesota, Minneapolis, MN, USA
e-mail: drek0002@umn.edu

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back pain [5]. Fever is generally absent, and if present suggests upper urinary tract involvement (pyelonephritis). The combination of dysuria and frequency, combined with absence of vaginal discharge or irritation, has a positive predictive value for UTI of greater than 90% [6]. The presence of a vaginal discharge or irritation lowers this value substantially and should prompt consideration of other entities, including urethritis due to herpes simplex virus, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis,* and vaginitis due to *Candida* and *Trichomonas* species [1, 4].

The distribution of microorganisms that cause cystitis is highly predictable: 75–90% of cases are due to *Escherichia coli*, 5–10% to *Staphylococcus saprophyticus*, and the remainder to other Gram-negative bacilli (e.g., *Proteus, Klebsiella*, and *Enterobacter*) and *Enterococcus* species [1, 4]. Knowledge of local susceptibility profiles (particularly for *E. coli*) can be combined with this predictable spectrum of organisms to guide the selection of empiric therapy for patients in whom cystitis is strongly suspected, thereby limiting inconvenience as well as costs of diagnostic testing to the patient. Risk factors for infection with *E. coli* resistant to trimethoprim/sulfamethoxazole (TMP–SMX) should be kept in mind when considering empiric therapy; these include recent use of TMP–SMX, foreign travel, and Hispanic or Asian descent [4].

2.2 Diagnosis

Women who have previously experienced cystitis can reliably predict a subsequent episode based on symptoms alone [7]. For such patients, telephone-based protocols (usually involving a nurse with a standardized questionnaire) can provide effective management while significantly reducing diagnostic testing and time spent by the patient and clinician. Patient-initiated therapy at the onset of symptoms is also effective, especially for women with recurrent episodes of cystitis. For women with a first episode of UTI or those in whom the diagnosis of UTI is uncertain, analysis for pyuria with either a rapid test for leukocyte esterase or a urine microscopy may be indicated. In the setting of typical UTI symptoms, a positive dipstick or microscopy test result has a high positive predictive value and provides sufficient evidence to diagnose UTI and initiate therapy [4]. Urine culture is generally not indicated for an initial episode of uncomplicated cystitis (i.e., cystitis occurring in the absence of host factors that predispose a patient to UTI, make UTI more difficult to treat, or shift the spectrum of causative microorganisms; as discussed below). However, if there is a history of recurrent UTI or recent antimicrobial therapy, a culture may be beneficial to screen for antimicrobial resistance. Post-therapy testing of any sort is not useful in the absence of clinical symptoms and should be discouraged [1].

2.3 Therapy

Knowledge of local antimicrobial resistance patterns is essential for selecting appropriate therapy. In settings where the prevalence of TMP–SMX resistance in *E. coli* is known to be <20%, TMP–SMX is the preferred first-line agent for uncomplicated

Table 1 Antimicrobial agents, dose, dosing interval, and duration of treatment for uncomplicated cystitis in women

Drug and dose	Dosing interval	Duration	Comments
Trimethoprim–sulfamethoxazole 160/800 mg	q12 h	3 days	1st line, if local TMP–SMX resistance prevalence < 20%
Ciprofloxacin 250 mg	q12 h	3 days	Alternative if TMP–SMX resistance prevalence >20% available in generic formulation, thus preferred over other fluoroquinolones for cost reasons
Nitrofurantoin monohydrate/macrocrystals 100 mg	q12 h	5 days	Alternative if local TMP–SMX or fluoroquinolone resistance prevalence > 20% or TMP–SMX allergy
Fosfomycin 3 g	Single dose	NA	3rd-line; resistance uncommon
Amoxicillin–clavulanate 250/125 or 500/125 mg	q8 h (250/125 mg) to q12 h (500/125 mg)	7 days	Alternative with TMP–SMX and fluoroquinolone resistance
Amoxicillin, 250 or 500 mg	q8 h (250 mg) to q12 h (500 mg)	7 days	Useful in pregnancy and for enterococcal UTI

cystitis (Table 1) [1]. In the absence of conditions that classify a UTI as complicated (see below), 3 days of therapy has been shown to be as effective as 7 days, with the advantages of decreased costs and fewer adverse effects. Single-dose therapy offers the appeal of decreasing costs even further; however, single-dose treatment is associated with failure rates higher than those observed with 3- and 7-day therapy and is not recommended. In areas where the *E. coli* resistance prevalence to TMP–SMX is known to exceed 20% or if the patient has risk factors for TMP–SMX resistance, alternative agents to which susceptibility is more likely should be used for empiric therapy [1]. Options include 3-day therapy with a fluoroquinolone or, alternatively, 5 days of nitrofurantoin (Table 1) [8, 9]. Because of the value of fluoroquinolones' in treating pyelonephritis and other serious infections due to Gram-negative bacilli, fluoroquinolones should be used sparingly for uncomplicated cystitis. Nitrofurantoin has remained active against most uropathogens even after decades of use, and when given for 5 days for cystitis has similar efficacy to 7 days of TMP–SMX [8]. Another option is single-dose fosfomycin; however, success rates are lower than the options discussed above, making this a third-line agent [10].

3 Pyelonephritis

3.1 Definition, Presentation, and Epidemiology

Pyelonephritis implies infection of the kidney and the renal pelvis. The classic manifestations are flank pain and tenderness accompanied by fever. A wide range of other

signs and symptoms may be present, ranging from dysuria, nausea, and malaise to severe sepsis and septic shock. In patients with symptoms suggestive of cystitis, but who also have indicators of a more systemic disease, the diagnosis of pyelonephritis (or its analog, febrile UTI) should be considered [4]. The causative organisms of pyelonephritis are similar to those in cystitis, except that *S. saprophyticus* is less common. *E. coli* remains the most frequently isolated pathogen, while other Gram-negative bacilli are less common. Among the Gram-positive organisms, enterococci and *S. aureus* occasionally cause pyelonephritis but are quite uncommon in the absence of an indwelling urinary device [1, 4].

3.2 Diagnosis

The diagnosis of pyelonephritis should be made clinically, based primarily on history and physical examination, with initial supporting laboratory evidence from a urinalysis or Gram's stain demonstrating pyuria or bacteriuria [4]. In addition, because of the severity of illness, a pretreatment urine culture should be obtained for all patients suspected of having pyelonephritis [1]. A Gram's stain of unspun urine can be helpful in selecting an initial antimicrobial regimen, although in patients with less than 10^3 organisms/mL of urine, this test may be falsely negative and should not be used to rule out pyelonephritis [11]. Blood cultures are positive in a substantial percentage of patients with pyelonephritis; however, they provide little additional information beyond what is obtained from a pre-therapy urine culture and can be omitted from the routine evaluation for pyelonephritis unless another diagnosis for which they are relevant is being considered [4].

Additional laboratory testing or imaging should be ordered only if the results would aid in patient management. For example, measurement of serum creatinine to estimate renal function can facilitate appropriate dosing of antimicrobials. In contrast, routine imaging of the kidneys and collecting system with either computerized tomography (CT) or ultrasonography contributes substantially to the cost of treating pyelonephritis, with little evidence of clinical benefit in most patients [3, 12]. In case of diagnostic uncertainty, contrast-enhanced CT is the preferred imaging modality since it has high sensitivity for detecting pyelonephritis and other potential causes of the patient's clinical manifestations. CT is also the test of choice to evaluate for complications such as a perinephric or intra-renal abscess, so should be considered if the patient's condition has not improved appreciably after 48 h of treatment with an appropriate antimicrobial agent [12]. Post-therapy urine cultures have no established clinical value, so should not be done routinely.

3.3 Therapy

The treatment of pyelonephritis should include consideration of the appropriate antimicrobial regimen and duration of therapy. Outpatient therapy in appropriate patients is a potentially safe and cost-effective approach. Substantial published

experience indicates that patients with pyelonephritis, who have mild-to-moderate symptoms, can be treated successfully as outpatients with oral antimicrobials, with or without an initial dose of parenteral therapy and with intravenous volume repletion in the Emergency Department [4]. Indications for hospital admission include hypotension, nausea, vomiting, and tachycardia unresponsive to initial fluid administration as well as inability of the patient to obtain timely medical care if symptoms later worsen. Patients who lack these features can be considered candidates for outpatient therapy, whereas those exhibiting any of these features (or who have other clinical manifestations suggestive of more severe disease) may need extended observation to ensure clinical improvement prior to discharge from the Emergency Department with oral therapy or may require hospital admission [1].

For most patients with mild-to-moderate pyelonephritis, oral antibiotics can be used from the outset, provided there is no recent history of UTI with an organism resistant to all oral options and if vomiting or nausea does not threaten the reliability of the oral route. In contrast, patients who are sufficiently ill to warrant hospitalization should generally be initiated on intravenous therapy followed by conversion to an oral regimen once symptoms have improved sufficiently that oral therapy is feasible (i.e., nausea and vomiting are resolved or controlled, and hypotension and tachycardia have been corrected). Waiting for final urine culture and susceptibility results is unnecessary before choosing an oral regimen, if the patient is clinically ready for oral antimicrobials [1, 4].

Empiric therapy, whether intravenous or oral, should be selected based on the likely causative microorganisms and local susceptibility profile, if known. Because community-acquired pyelonephritis is usually caused by *E. coli* [1], suitable empiric therapy options include oral and intravenous fluoroquinolones, intravenous third-generation cephalosporins, and aminoglycosides (Table 2) [4]. In most of the United States, the prevalence of TMP–SMX resistance among uropathogens is high enough that TMP–SMX is inappropriate for empiric therapy for pyelonephritis. However, if testing shows that the isolated organism is susceptible, TMP–SMX is an excellent option for completion of therapy [13]. Patients with recent urologic surgery, indwelling foreign material (i.e., ureteral stents, urinary catheter, or percutaneous nephrostomy tubes), or other complicating conditions have an increased likelihood of resistant uropathogens such as *Pseudomonas* and enterococci [1]. For such patients a carbapenem or beta-lactam/beta-lactamase inhibitor combination may have a role for initial therapy, especially if the urine Gram's stain suggests enterococci. An aminoglycoside (plus ampicillin, if *Enterococcus* is suspected) offers similarly broad Gram-negative coverage, but lower costs, compared with newer agents such as carbapenems.

In some regions of the United States, resistance among uropathogens to carbapenems, fluoroquinolones, and beta-lactam antibiotics is becoming increasingly prevalent, whereas resistance to aminoglycosides has remained uncommon [14]. Certainly, the aminoglycosides' favorable resistance profile, high achievable drug concentrations in renal tissue, and comparatively low cost must be weighed against their nephro- and ototoxicity potential [1]. However, because aminoglycoside toxicity typically develops only after several days of therapy, and given that most

Table 2 Antimicrobial agent, dose, dosing interval, route of administration, and duration of treatment for uncomplicated pyelonephritis

Drug and dose	Dosing interval	Route of administration	Duration of therapy	Comments
Ciprofloxacin 400 mg	q12 h	Intravenous	Variable[a]	Available in generic formulation
Ciprofloxacin 500 mg	q12 h	Oral	7 days	Equivalent to intravenous route if functioning GI tract; available in generic formulation
Ceftriaxone 1 g	q24 h	Intravenous	Variable[a]	Cost-effective option for initial therapy
Gentamicin 3–5 mg/kg[b]	q24 h	Intravenous	Variable[a]	Initial therapy (often combined with ampicillin); favorable resistance profile; anti-*Pseudomonas* activity; alternative if penicillin or cephalosporin allergy
Ampicillin 1 g[c]	q6 h	Intravenous	Variable[a]	Combined with gentamicin for enterococcal activity
Trimethoprim–sulfamethoxazole 160/800 mg	q8 h–q12 h	Intravenous/oral	10–14 days	Cost-effective option if organism sensitive; not suitable for empiric therapy in most locations due to resistance concerns
Amoxicillin 875 mg	q12 h	Oral	10–14 days	Useful in pregnancy and for enterococcal UTI; not suitable for empiric therapy
Amoxicillin/clavulanate 875/125 mg	q12 h	Oral	10–14 days	Useful in pregnancy and for enterococcal UTI; many *E. coli* are resistant
Aztreonam 1 g	q8 h–q12 h	Intravenous	Variable[a]	Alternative for penicillin or cephalosporin allergy
Cefepime 1 g	q8 h–q12 h	Intravenous	Variable[a]	Anti-*Pseudomonas* activity
Imipenem/cilastatin 500 mg	q8 h	Intravenous	Variable[a]	Initial therapy (for complicated or severe disease); available as a generic formulation in 2009
Pipercillin/tazobactam 3.375 g	q6 h	Intravenous	Variable[a]	Initial therapy (complicated or severe infection)

[a]Most patients can be transitioned from an intravenous regimen to an oral regimen, see text for details.
[b]Can combine with ampicillin if suspicion for enterococci is high.
[c]Combine with gentamicin if used for empiric therapy.

patients can be switched to a non-aminoglycoside regimen before this point, toxicity concerns can often be avoided.

Duration of antibiotic therapy should be determined by the following: balance between clinical effectiveness, the risk of adverse events, and the emergence of resistance. Fluoroquinolones can be effective with short courses of therapy compared to other agents [1]. Levofloxacin 750 mg daily for 5 days or ciprofloxacin 500 mg twice daily for 7 days usually provide excellent clinical efficacy in treating pyelonephritis [4]. Whether the favorable results observed with 5 days of high-dose levofloxacin can be extrapolated to a similar regimen with ciprofloxacin is unknown. The levofloxacin regimen's once-daily dosing and slightly shorter overall duration must be weighed against its generally greater cost per dose, since ciprofloxacin is now available in the United States as a generic formulation. Non-fluoroquinolone-based therapy for pyelonephritis should be given for a longer duration, generally 10–14 days, and this time may require adjustment based on individual patient characteristics (Table 2) [4].

4 Complicated UTI

The designation complicated UTI implies the presence of host characteristics that make UTI more likely, reduce the effectiveness of therapy, or predispose toward less virulent, but often more antimicrobial-resistant, causative microorganisms [4]. Such host characteristics include specific medical conditions (most importantly diabetes mellitus) and functional and anatomical abnormalities of the urinary tract. Male sex is often regarded as a criterion for complicated UTI; however, a subset of men with cystitis (generally, those who are younger and otherwise healthy) appear to respond well to the shorter courses of therapy which are traditionally reserved for uncomplicated cystitis in women [1]. Of note, UTI caused by a resistant organism is not per se classified as complicated because therapy with an agent to which the organism is susceptible will generally produce clinical success without the need to extend therapy.

The approach to diagnosing and initiating empiric treatment of complicated UTI, whether cystitis or pyelonephritis, is similar to that for uncomplicated UTI, with two important caveats. First, treatment of complicated cystitis may be more effective when guided by pre-therapy urine cultures, although this has not been adequately studied. Second, the initial antimicrobial regimen for complicated UTI should be broader spectrum than for uncomplicated infections, since the range of etiologic agents is wider and antimicrobial resistance is more likely [5]. For cystitis, initial therapy often entails using a fluoroquinolone as a first-line agent, whereas for pyelonephritis an initial regimen with anti-pseudomonal activity is reasonable. Cost savings may be achievable by appropriately changing therapy to the most economical agent that has activity against the isolated pathogen (once culture results are available) and by using oral agents in the outpatient setting when feasible.

5 Recurrent UTI

5.1 Definition and Epidemiology

Recurrent UTI is commonly defined as two episodes of UTI which occur within 6 months [15]. Up to 20–30% of women experience recurrent UTI at some point in their lifetime [7]. Among premenopausal women, risk factors for recurrence include use of spermicide-based contraception, female gender, and being a nonsecretor of blood group substances [15], whereas risk factors among postmenopausal women include decreased level of estrogen, incontinence, presence of a cystocele, and post-voiding residual urine [15]. The microbiology of recurrent UTI depends heavily on the presence or absence of underlying complicating conditions (as discussed above for complicated UTI) [4].

5.2 Prevention

Several inexpensive approaches can reduce the frequency of recurrent UTI. These include avoidance of spermicide-based contraception methods, use of topical estrogen therapy in postmenopausal women to help restore a lactobacillus-dominated premenopausal vaginal flora, antimicrobial prophylaxis (whether continuous, intermittent, or post-coital), and patient-initiated antimicrobial therapy for UTI [15]. In addition, daily intake of cranberry products may be an effective non-pharmacologic aid for decreasing the frequency of symptomatic UTI [16]. However, in a recent Cochrane Database systematic review of cranberry ingestion to decrease UTIs, dropout rates in the reviewed trials were high, the beneficial effect was weaker in elderly subjects, and the total number of included subjects was relatively small ($n = 1{,}049$) [16]. Therefore, the reliability and applicability of these findings must be interpreted with caution. For patients with recurrent UTI, investigation for an underlying structural abnormality has been traditionally recommended; however, in otherwise healthy women, such testing is generally unhelpful unless the recurrent infections are of unusual severity, occur shortly after completing an appropriate course of therapy, or are caused by seemingly identical microorganisms.

6 Catheter-Associated UTI

6.1 Definition, Presentation, and Epidemiology

Management of catheter-associated UTI (CAUTI) can be challenging. The vast majority of clinical episodes that are labeled as CAUTI are actually catheter-associated bacteriuria/funguria (CAB/F) occurring in the absence of symptoms or other clinical manifestations of infection, which therefore should not be diagnosed or treated [17, 18]. Bacterial (and fungal) colonization of indwelling catheters, including urethral and suprapubic catheters and percutaneous nephrostomy tubes,

occurs in a time-dependent manner, such that by 1 month after catheter insertion virtually all catheterized patients will have a positive urine culture (i.e., will have CAB/F) [18]. A minority of patients with CAB/F will develop clinical manifestations, which can range from suprapubic discomfort to overt urosepsis. The clinical significance of CAB/F can be difficult to determine if the patient has sensory impairment, if the patient has altered mental status, or if the patient has difficulty in communicating symptoms.

6.2 Prevention

Prevention of CAB/F, and by extension CAUTI, is best approached by limiting the use of indwelling drainage devices. It is important that clinicians maintain strict adherence to the principle of not obtaining a urine culture in the absence of clinical manifestations that could plausibly be attributed to UTI in these patients. The presence of urine sediment, increased urine concentration, and malodor are not by themselves indicative of CAUTI (or CAB/F) and should not be used as a rationale for obtaining a urine culture [4].

Methods to limit indwelling drainage devices include automated stop orders for catheters, daily reminders to clinicians that a catheter is in place, and daily checklists that include assessment of the need for all indwelling devices. Alternatives to indwelling catheters include intermittent catheterization, external (condom or bag) catheters in suitable patients, and absorbent pads/garments. Antimicrobial-coated catheters have been demonstrated to reduce CAB/F in short-term catheterized patients but not to prevent symptomatic CAUTI or to reduce costs, antimicrobial use, or length of hospital stay [18].

6.3 Treatment

Treatment of CAUTI should be limited to patients who are experiencing symptoms or displaying clinical manifestations that could plausibly be attributed to UTI [4]. In a catheterized patient whose symptom reporting is unreliable but who exhibits other manifestations possibly due to UTI, a thorough evaluation for other potential causes should be undertaken prior to attributing the patient's syndrome to CAUTI.

If CAUTI is diagnosed and treated with antimicrobials, replacement (or, better still, removal) of the catheter leads to more rapid sterilization of the urine, although if the catheter is replaced, renewed colonization will likely recur within the next 4 weeks [19]. Antimicrobial therapy should initially be chosen based on a urine Gram's stain, local resistance profiles, and the results of any recent urine cultures. When culture results become available, the most appropriate agent should be chosen to complete therapy (as discussed above). Because the presence of an indwelling catheter defines the UTI as complicated, treatment should be for 10–14 days if the catheter remains in use. If the catheter is removed and no other complicating condition is present, then shorter duration therapy (3–5 days) may be appropriate [4].

7 Asymptomatic Bacteriuria

7.1 Definition, Etiology, and Therapy

Asymptomatic bacteriuria (ABU) is important to discuss both to highlight the few specific circumstances in which antimicrobial therapy is indicated and to reiterate that, in the majority of cases, therapy offers no benefit and should not be given. Adherence to these principles avoids the costs and risks of unnecessary drug therapy and avoids drug-related adverse effects and emergence of drug-resistant infections.

Asymptomatic bacteriuria can occur in any patient population but is most common among the elderly (particularly in long-term care facilities), individuals who perform intermittent urinary catheterization, and patients with long-term indwelling catheters among whom ABU is essentially universal [20]. In such patients, ABU is generally benign and is best ignored. The only patients who should be tested and treated for ABU are pregnant women and patients undergoing a urologic procedure with anticipated mucosal disruption.

Pregnant women with ABU have a high risk of progressing to pyelonephritis, which can be reduced by treatment of the ABU [21]. A posttreatment urine culture should be obtained to ensure eradication. Patients undergoing a tissue-invasive urologic procedure in the presence of ABU are at risk for secondary urosepsis. Whether such procedures should be delayed until urine sterility has been confirmed or can proceed safely under appropriate antimicrobial coverage is undefined.

Optimal duration of antimicrobial therapy for ABU is unknown, but in pregnancy it is common to treat for the same duration as for uncomplicated cystitis (Table 1) [21]. Treatment duration in patients scheduled for urologic procedures depends partly upon whether an indwelling catheter remains in place postprocedure. If no catheter is used, then therapy can be stopped the day after the procedure, whereas if a catheter is retained treatment may be extended.

8 Summary

The single intervention with the greatest potential for optimizing management of UTI is to limit diagnostic testing and antimicrobial therapy to those patients who have relevant clinical manifestations. The only exceptions to this rule involve pregnancy and pre-urologic-procedure ABU. Strict adherence to this principle combined with rational testing, triaging of patients to the appropriate level of care, and conversion to oral therapy as rapidly as possible in patients initially given parenteral therapy are all important steps in providing effective therapy for UTI.

Key Points

- Testing and treatment for UTI should be driven by symptoms and signs, except in a few narrowly defined clinical settings (i.e., during pregnancy and prior to invasive urological procedures).

- Treatment should be evidence based, taking into account local antimicrobial resistance patterns and risk factors for resistant urine organisms, especially *E. coli*.
- For uncomplicated cystitis, empiric therapy with 3 days of TMP–SMX is preferred.
- When resistance to TMP–SMX is likely or TMP–SMX is otherwise contraindicated, nitrofurantoin for 5 days is an effective fluoroquinolone-sparing treatment option for cystitis.
- Systemic measures to minimize the placement of indwelling urinary catheters and to facilitate the prompt removal of those that are placed can reduce the incidence of CABF and CAUTI.

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Sexually Transmitted Diseases

Alice C. Thornton, Bojana Stevich, Janet N. Arno, and Barbara Van Der Pol

1 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 public STD clinics; according to the Center for Disease Control's (CDC) STD Treatment Guidelines. This emphasizes the need for all clinicians to be aware of and to provide management for STDs [1]. 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. A grave consequence of STDs is the associated 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 [2, 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, thus risking that the index patient will be re-exposed. A coordinated approach to treat both patient and partner is needed to effectively respond to STDs.

Risk assessment (including sexual history) and clinical evaluation are essential components of effective STD management. 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.

A.C. Thornton (✉)
Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine, Lexington, KY, USA
e-mail: thornton@uky.edu

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Evaluation should include questions on specific exposures such as a new partner, a partner experiencing discharge, or personal/partner use of intravenous drugs. STD practice guidelines also advise obtaining history of serologic testing for syphilis and HIV as well as inquiries about hepatitis B vaccination. 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 likelihood of certain STDs.

Clinical evaluation should also include a review of systems targeting the genitourinary tract. 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).

STD management goals include microbiologic cure, alleviation of signs and symptoms, prevention of sequelae, and prevention of transmission [1]. In most settings, instituting treatment for a symptomatic patient based on symptoms (presumptive diagnosis) is appropriate. The remainder of case management is preventive and involves the following: contact (partner) notification and treatment, counseling on risk reduction (condom promotion), and efforts to facilitate treatment compliance [1], 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. The Advisory Committee for HIV and STD Prevention (ACHSP) has made the following recommendations regarding screening [4]:

All sexually active women under the age of 25 years 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, exchange sex for money or drugs, are incarcerated, or use illicit drugs).
- Persons already infected with HIV should be screened routinely for STDs.

2 Disease 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 [1]. In developing countries, the differential broadens to include chancroid, donovanosis, and lymphogranuloma venereum (LGV). Other causes of ulcerative lesions that should be considered are trauma, malignancy, fixed drug eruption, and Behcet's and Reiter's syndromes. Multiple studies have shown that genital ulcer disease (GUD) is a risk factor for the acquisition of HIV infection [2].

In practice, it is often difficult to differentiate among the GUDs. 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 PCR test for herpes simplex virus (HSV), and a culture for *Haemophilus ducreyi*. Even after diagnostic evaluation, 25% of patients with GUD will not have a laboratory-confirmed diagnosis [1]. A multiplex polymerase chain reaction (PCR) with a sensitivity that exceeds 95% [1] is commercially available.

2.1 Chancroid

2.1.1 Clinical Description

The classic presentation of chancroid is an undermined, painful, purulent ulcer with ragged edges; however, clinical diagnosis is unreliable and insensitive. After an incubation period of 4–7 days, the initial lesion appears. It is a tender erythematous papule that becomes a pustule and eventually erodes into an ulcer. Painful inguinal adenitis is commonly present [1].

2.1.2 Epidemiology

Chancroid is the most common GUD in many developing countries. Although not as common in the United States, outbreaks have occurred in major cities of industrialized countries. Risk factors associated with chancroid acquisition appear to be related to low socioeconomic status, geographic origin, drug use, commercial sex, and lack of circumcision. During epidemics, prostitutes have been the usual reservoir. Sexual contact is the only mode of acquisition and there is no asymptomatic reservoir.

2.1.3 Etiology

H. ducreyi, the etiologic agent of chancroid, is a Gram-negative facultative anaerobic bacillus that requires breaks in the epidermis or trauma to establish disease.

2.1.4 Diagnosis

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 serologic testing), a clinical presentation typical for chancroid, and negative HSV testing [1, 5]. The recommended treatment regimens for chancroid are summarized in Table 1.

Table 1 Treatment of chancroid [1]

Treatment	Duration
Azithromycin 1 g orally	Single dose
Ceftriaxone 250 mg intramuscularly (i.m.)	Single dose
Ciprofloxacin 500 mg orally 2 times a day	3 days
Erythromycin base 500 mg orally 4 times a day	7 days

2.1.5 Treatment

Treatment failures and development of resistance have been reported for chancroid. Decreased response to therapy has been noted in uncircumcised men and in HIV-infected individuals [1, 5]. 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 [1].

Development of resistant *H. ducreyi* is a concern. Plasmid-mediated, antimicrobial resistance has been described for ampicillin, sulfonamides, chloramphenicol, tetracycline, streptomycin, and kanamycin. Ceftriaxone is acceptable therapy for chancroid in the United States. However, one study in Kenya showed a reduced cure rate using ceftriaxone (73%) [6]. The macrolides and quinolones all have excellent in vitro activity against *H. ducreyi* [7]. A strain of *H. ducreyi* in Thailand with intermittent susceptibility to ciprofloxacin has been reported, suggesting that surveillance for development of quinolone-resistant strains is warranted [7]. Owing to high failure rates and increasing resistance, neither trimethoprim–sulfamethoxazole nor amoxicillin–clavulanic acid should be used for the treatment of chancroid [1, 5, 7].

2.2 Herpes Simplex Virus

Genital herpes simplex virus (HSV) infection is a disease of major public importance. Prevalence of HSV markedly increased throughout the world in the last four decades. This disease is a great concern to patients and health-care providers because of its morbidity, high recurrence rates, and complications such as aseptic meningitis and neonatal transmission.

2.2.1 Clinical Description

There are two antigenic types of HSV: HSV-1 and HSV-2. Most people with either HSV-1 or HSV-2 infection have subclinical disease and can be identified only by antibody status. Although HSV-1 has been historically associated with nongenital lesions, both HSV types can cause genital lesions [1]. 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 [8]. Routine viral culture with typing is recommended to aid in properly counseling patients [8]. The sensitivity of viral culture is low and therefore failure to isolate HSV does not rule out infection [1]. A swab from the base of the genital lesion can be assessed for HSV by viral culture, HSV antigen detection, or PCR of HSV DNA [1, 9]. Serologic testing can be used to identify HSV infection in the absence of lesions or with negative virus detection tests. Type-specific IgG testing directed against glycoprotein G of HSV-1 or that of HSV-2 can distinguish HSV-1 from HSV-2 [1, 9]. At the present time the most accurate test for serologic diagnosis of HSV-1 and HSV-2 infection is Western blot, with a sensitivity of >98% and a specificity >98% for distinguishing HSV-1-specific and HSV-2-specific antibodies.

Manifestations of HSV are variable, and many people have mild or unrecognized symptoms. Primary genital herpes infection occurs in HSV-seronegative individuals who never had either type of HSV. The first episode of Nonprimary genital herpes occurs in patients who had previous HSV-1 and now have HSV-2 genital infection. Primary genital herpes is characterized by more constitutional symptoms (fever, headache, and myalgias) and prominent localized symptoms (pain, dysuria, and tender inguinal adenopathy) [9]. Infection can also manifest as aseptic meningitis, transverse myelitis, urinary retention, monoarticular arthritis, hepatitis, thrombocytopenia, and extragenital lesions. These symptoms usually last for 12–20 days. HSV lesions start as bilateral papules or vesicles that eventually coalesce into area of ulceration. Cervicitis with asymptomatic viral shedding is common with HSV. Yeast vaginitis is frequently encountered in the initial HSV outbreak and bacterial superinfection is uncommon in the normal host. The most common cause of nongonococcal proctitis in men is HSV proctitis, which is another clinical manifestation of HSV. Recurrent genital herpes infections have shorter duration of lesions and also cause more localized and limited systemic symptoms.

2.2.2 Treatment

Pharmacotherapy is an important part of management of genital herpes (Tables 2, 3) and focuses on the use of three nucleoside analogs: acyclovir, valacyclovir, and famciclovir [1, 9]. All three drugs have been shown to reduce the duration and severity of primary and recurrent attacks of genital herpes [1, 9]. Topical acyclovir is not recommended, as it is less effective than oral acyclovir [1]. Antiviral therapy is recommended for all patients with clinical first-episode genital HSV [1, 8, 9].

Table 2 Treatment of HSV infection [1]

First clinical episode of genital herpes	Acyclovir 400 mg orally three times/day for 7–10 days or Acyclovir 200 mg orally five times/day for 7–10 days or Famciclovir 250 mg orally three times/day for 7–10 days or Valcyclovir 1 g orally twice/day for 7–10 days
Suppressive therapy for recurrent genital herpes	Acyclovir 400 mg orally twice/day or Famcyclovir 250 mg orally twice/day or Valcyclovir 500 mg orally once/day or Valcyclovir 1 g orally once/day
Episodic therapy for recurrent genital herpes	Acyclovir 400 mg orally three times/day or Acyclovir 800 mg orally twice/day for 5 days or Acyclovir 800 mg orally three times/day for 2 days or Famcyclovir 125 mg orally twice/day for 5 days or Famcyclovir 1,000 mg orally twice/day for 1 day or Valcyclovir 500 mg orally twice/day for 3 days or Valcyclovir 1 gm orally once/day for 5 days

Table 3 Treatment of genital herpes in persons infected with HIV [1]

Recommended regimens for daily suppressive therapy	Acyclovir 400–800 mg orally twice to three times/day or Famciclovir 500 mg orally twice/day or Valcyclovir 500 mg orally twice/day
Recommended regimens for episodic infection	Acyclovir 400 mg orally three times/day for 5–10 days or Famcyclovir 500 mg orally twice/day for 5–10 days or Valcyclovir 1 gm orally twice/day for 5–10 days

Two basic strategies are used for treatment of recurrent genital herpes: episodic therapy and suppressive therapy (Table 2). Episodic therapy involves treating individual episodes when they occur; the goal in episodic therapy is to initiate treatment as soon as possible after onset of symptoms. Daily suppressive therapy is used for patients with frequent recurrences ($\geq$6 episodes per year), severe physical or emotional distress, or potential for transmission to sexual partners [1]. Even though breakthrough episodes may occur on suppressive therapy, all three drugs may effectively reduce recurrences by up to 75% [1]. Daily treatment with oral acyclovir reduces but does not eliminate subclinical shedding of HSV.

Resistance of HSV to acyclovir in vitro is $\sim$3%, but long-term suppression in an immunocompetent host does not appear to select resistant virus [10]. Usually acyclovir-resistant HSV infection in the immunocompetent patient is not associated with clinical failure, even though rare, such cases have been reported [10]. Most acyclovir-resistant HSV infections occur in immunocompromised hosts. Development of resistance to acyclovir occurs at the rate-limited step of the enzyme

thymidine kinase (TK). Mechanisms of resistance to acyclovir are due to either TK deficiency, which is the most common, or alteration in TK or DNA polymerase [9, 10]. Famcyclovir and valcyclovir have a similar mechanism of action, so most acyclovir-resistant strains are also resistant to famcyclovir and valcyclovir. Even though susceptibility testing for HSV isolates is not routinely recommended, if lesions persist in a patient receiving acyclovir, resistance of the HSV strain should be suspected and susceptibility testing should be considered [1]. Acyclovir-resistant HSV infections usually require treatment with alternative agents, such as foscarnet, cidofovir, or trifluridine.

Foscarnet, which is a viral DNA polymerase inhibitor, has been used topically and parenterally in patients with acyclovir-resistant HSV infection. Success with topical 1% foscarnet cream has also been reported. Foscarnet is the preferred agent for acyclovir-resistant HSV infections despite its toxicity, including nephrotoxicity, electrolyte imbalance, and anemia. HSV infections that occur after foscarnet therapy can be either acyclovir susceptible or acyclovir resistant. Foscarnet-resistant HSV may develop after prolonged foscarnet use.

Cidofovir, a nucleotide analog, has been used with success in immunocompromised patients with acyclovir-resistant HSV infection. Topical cidofovir gel is preferred because of renal toxicity with intravenous cidofovir.

For the treatment of ophthalmic HSV infections, trifluridine, a nucleoside analog, can be used. Trifluridine demonstrated complete healing in 7 and partial healing in 14 patients out of 26 patients with HIV who had mucocutaneous HSV infection that was unresponsive to acyclovir [11].

Immunocompromised patients may have prolonged and severe recurrent genital herpes. Dissemination HSV disease requires treatment with 5–10 mg/kg of acyclovir intravenously (Table 2). HSV is a common clinical manifestation of HIV infection and most HIV-infected persons with HIV will respond to acyclovir. Most HIV patients with HSV infection will benefit from chronic HSV suppressive therapy. Acyclovir resistance is more common in immunocompromised than in immunocompetent individuals.

Pregnant woman with genital HSV may transmit their virus to their newborns. 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 as opposed to those mothers with new HSV-2 but previous HSV-1 infection (20%) [1, 9]. Mothers with established herpes infection have the lowest risk of transmission to the neonate (<1%). Therefore, prevention of neonatal herpes should focus on prevention of acquisition of new genital HSV infection during late pregnancy. Women who are HSV-2 or HSV-1 seronegative and who have seropositive partners are susceptible to HSV infections and should be counseled to avoid unprotected genital or oral sexual contact during late pregnancy. At the onset of labor, all women should be examined and interviewed regarding genital herpes; those with no clinical evidence of lesions can be delivered vaginally [1]. Controversy remains regarding antiviral therapy during pregnancy. Some studies have used acyclovir 400 mg orally t.i.d. or valacyclovir 500 mg b.i.d. starting at 36-weeks of gestation for women with recurrent genital herpes [1, 9].

2.3 Syphilis

2.3.1 Clinical Description

Syphilis is a systemic infection with periods of active clinical disease and periods of latency. The primary state develops approximately 3 weeks from exposure and is characterized by a chancre (painless lesion) and bilateral nontender regional adenopathy [12]. The ulcerative lesion with well-circumscribed borders can be found at genital, perirectal, perianal, or nongenital sites. Untreated, the chancre heals in a few weeks. Secondary syphilis represents multiplication and dissemination of treponemes throughout the body. Occurring up to 6 months after the initial chancre, this state 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 nephritic syndrome may develop [12].

Persons with no clinical syndrome, but positive serologic tests, are said to have latent syphilis [1]. Early latency occurs during the first year of infection and late latency occurs more than 1 year from the initial chancre. Tertiary (late) syphilis develops in one-third of untreated patients 10–25 years after the initial infection [12]. Treponemes invade the central nervous system (CNS), cardiovascular system, eyes, skin, or other internal organs. Gummas, which are locally destructive lesions involving the liver, skin, bones, and other organs can develop [12]. During this state, transmission of syphilis to sexual contacts does not occur; however, sexual partners and infants born to mothers with any stage of syphilis should be evaluated according to the CDC guidelines [1].

2.3.2 Epidemiology

The incidence of syphilis in the United States has fluctuated, with peak rates occurring recently during the late 1980s. In 2000, syphilis incidence was at its lowest since 1941, at 2.1 per 100,000 population [13]. From 2001 to 2004, rates increased to 2.7 per 100,000, predominantly as a result of increases in cases among men who have sex with men (MSM) [13]. Syphilis remains more common in non-Hispanic blacks and is concentrated in the southern parts of the United States [13]. Increases in incidence of syphilis among MSM have been associated with high rates of HIV coinfection, high-risk sexual behavior, and use of drugs such as methamphetamines. Additionally, increases have occurred among MSM who used Internet chat rooms to contact sex partners [12, 13].

It is well recognized that syphilis facilitates transmission of HIV, and all patients with syphilis should be tested for HIV infection [1]. 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 blood-borne route (blood transfusion/needle sharing), nonsexual personal contact, and accidental direct inoculation.

2.3.3 Etiology and Diagnosis

T. pallidum, the etiologic agent of syphilis, is a spirochete that can be visualized by dark-field microscopy and silver staining. Dark-field examination or DFA tests of lesions or tissue are the methods used to make a definitive diagnosis of syphilis [1]. 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) [1]. 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) [14]. 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, or mycoplasmal infections as well as in the elderly, pregnant women, and intravenous drug users [15, 16]. 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 [16].

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 months after therapy for primary or secondary syphilis identifies persons at risk for treatment failure [1]. 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 [1]. Treponemal tests often remain reactive for the remainder of the patient's life regardless of disease activity and should not be used to assess clinical response [1]. PCR-based tests have been developed but are currently only available in the research setting [12].

2.3.4 Treatment

Penicillin G is the drug of choice for treatment of patients with all stages of syphilis (Table 4) [1]. Second-line therapies include tetracycline or erythromycin [1]. Although penicillin treatment for syphilis is the standard of care, no adequately conducted comparative trails 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 STD experts agree that single-dose ceftriaxone is not effective for treating syphilis [1]. There have been preliminary studies of azithromycin for treatment of patients with primary and secondary syphilis [17], but STD experts warn that azithromycin should be used

Table 4 Treatment of syphilis [1]

Stage	Drug	Dose	Duration	Comments
Primary/secondary (1°/2°)	Benzathine penicillin G	2.4 million units i.m.	1 time	
Nonpregnant penicillin allergic	Doxycycline or tetracycline	100 mg b.i.d	2 weeks	Follow closely
		500 mg. b.i.d	2 weeks	
Pregnant/penicillin allergic	Desensitize against penicillin then as for 1°/2°	As for 1°/2°	1 time	Consider fetal monitoring
Latent syphilis				
Early	As for 1°/2° above	As for 1°/2°	1 time	
Late	Benzathine penicillin G	2.4 million units i.m.	Three doses at 1-week intervals	
Nonpregnant penicillin allergic	Doxycycline or tetracycline	100 mg b.i.d 500 mg b.i.d.	4 weeks 4 weeks	
Pregnant/ penicillin allergic	Desensitize to penicillin	As for early/late	As for early/late	
Tertiary syphilis	Aqueous crystalline	3–4 million units i.v. q 4 h (18–24 million units total)	10–14 days	
	Penicillin G *or*		10–14 days	
	Procaine penicillin plus Probenecid	2.4 million units i.m. qd 500 mg po qid	10–14 days	
Penicillin allergic (both pregnant and nonpregnant)	Desensitize against penicillin	As for tertiary		

with caution. Currently, there are no recommendations for azithromycin as treatment for primary or secondary syphilis, due to the sustained success of penicillin G benzathine and reports of emergence of azithromycin-resistant *T. pallidum* [18].

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 postreatment and subsides within 24 h [12]. 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 months. 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 months after therapy or who have persistent signs or symptoms. These patients should be retreated and evaluated for the possibility of re-exposure, HIV co-infection, or neurosyphilis [1]. Unless reinfection is certain, a lumbar puncture should be performed in treatment failure to search for evidence of neurosyphilis, which requires more aggressive antibiotic therapy.

There is a high probability that an infectious syphilitic individual will infect his or her partner during sexual activity (50%). Persons who have been exposed within 90 days of the index case's diagnosis should receive presumptive treatment. Patients who were exposed >90 days prior to the index case's diagnosis should be evaluated, and if serologic tests are not available immediately and follow-up is uncertain, presumptive treatment should be given [1].

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 [19]. The serologic response of HIV patients was poorer, but there were few clinically defined failures in either group. 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 months after treatment is important in HIV patients [1]. 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 [1].

All pregnant women with syphilis should receive penicillin appropriate to their stage of disease (Table 4). 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 [1, 16]. The CDC recommends skin testing and desensitization in penicillin-allergic pregnant women requiring treatment for syphilis [1]. A manifestation of Jarisch–Herxheimer reaction is uterine contractions; therefore, some suggest fetal monitoring before initiation of penicillin therapy for patients in the third trimester [16]. There is no documented evidence of *T. pallidum* resistance to penicillin [14, 16].

2.4 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 weeks is recommended; further information can be found in the recent CDC guidelines [1].

3 Human Papilloma Virus

3.1 Clinical Description

Human papilloma virus (HPV) infections have two important clinical manifestations: external genital warts (EGWs) and squamous intraepithelial lesions [20, 21]. A discussion of these neoplasms is beyond the scope of this chapter but screening and treatment issues can be found elsewhere [1]. 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. The acetowhite test has not been definitely established as useful for diagnosis and has a low positive predictive value [1]. Biopsy is seldom needed and is reserved for atypical lesions, uncertain diagnosis, progression of disease during treatment, or warts that appear pigmented, indurated, ulcerated, or fixed to underlying structures [20].

3.2 Diagnosis

Because EGWs frequently occur on multiple genital sites, an entire examination of the genitalia is warranted. Speculum examination assessing for vaginal and cervical warts is recommended for women with warts in genital sites. Instrumentation (colposcopy, anoscopy, or urethroscopy) is recommended for examination of women with cervical warts, men and women with recurrent perianal warts (history of anoreceptive intercourse), or men with warts at the distal urinary meatus and terminal hematuria or abnormal stream [20]. The differential diagnosis of EGWs is broad and includes normal anatomic structures, acquired conditions (e.g., molluscum contagiosum), and neoplasms such as vulvar neoplasia [21].

3.3 Epidemiology

An estimated 24 million Americans are infected with HPV [3]. Surveillance systems for HPV are rudimentary. Most experts agree that approximately 1% of the adult population has symptomatic EGWs [20]. Genital HPV is transmitted primarily sexually; however, perinatal transmission can occur (laryngeal papillomatosis) [21]. Immunocompromised patients such as HIV-seropositive patients and organ transplant recipients are at high risk for genital HPV infection [20]. An association between increasing number of sex partners and detection of HPV has been noted [21]. There is inconclusive data on the association between smoking or estrogen stimulation (oral contraceptives or pregnancy) and HPV infection.

3.4 Etiology

There are over 100 HPV genotypes, divided into low risk (including 6 and 11) and high risk (e.g., 16, 18, 31, 33, 35) based on their association with anogenital cancers [1, 20, 21]. Visible EGWs are generally caused by types 6 and 11 and have also been associated with laryngeal warts [20].

3.5 Treatment

The primary goal of treatment of EGWs is to relieve symptoms and remove symptomatic warts [20]. There is no evidence that treatment eradicates HPV or decreases infectivity [1, 20]. 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 with 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 [1, 20].

Treatment is divided into patient-applied (podofilox and imiquimod) and provider-administered (cryotherapy, podophyllin resin, trichloroacetic, or bichloroacetic acid [TCA/BCA] interferon and surgery) therapies (see Table 5). Podofilox and podophyllin are antimitotic agents. Imiquimod is an immune response-enhancing agent that induces macrophages to secrete cytokines [20]. Cryotherapy with liquid nitrogen freezes and kills EGW-affected tissues,

Table 5 Treatment of genital warts[a]

Therapy	Dose	Duration	Comments
Patient-applied Podofilox	0.5% solution/gel	Up to 4 cycles	Applied with finger or cotton swab Apply b.i.d for 3 days then 4 days of no therapy (one cycle)
Imiquimod	5% cream	Up to 16 weeks	Apply with finger 3 times a week
Provider-applied cryotherapy	Liquid nitrogen/ cryoprobe	Repeat applications every 1–2 weeks	
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
Office surgery (curettage, electrosurgery, or scissor excision)			
Alternative treatments			
Intralesional interferon	1×10^6 International units (IU)	Three times weekly	Can cause flu-like symptoms, stinging, burning, and pain
Laser surgery			May require general anesthesia

[a]Safety in pregnancy is not established.

which results in sloughing and wart destruction [20]. TCAs/BCAs are caustic agents that destroy warts by chemical coagulation of proteins. Due to the low viscosity of these agents, care must be taken to prevent the solution from running onto unaffected areas (treated areas should be allowed to dry before the patient sits or stands) [1]. Surgical removal includes curettage, electrocautery/electrotherapy, and ablative therapy (laser). Intralesional injections or interferon administered topically have not been shown to be effective as a primary or adjunct therapy for EGWs [20]. Cidofovir and 5-fluorouracil (5-FU/ipinephrine/bovine collagen gel) cream are under development.

There are no guidelines regarding which treatment to use first for EGWs. Choice of modalities should be guided by patient preference number and location of warts, and the patient's ability to follow directions, and clinical expertise [1]. 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 the manufacturer's recommendations [1]. Clinicians must monitor patient progress and avoid overtreatment. There is no single treatment modality that is vastly superior to other therapies [20]. All wart treatments may cause mild local irritation, ulceration, or erosion. Ablative modalities can result in hypopigmentation, hyperpigmentation, or scarring. Pregnancy and immunodeficiency can be associated with larger or more numerous EGWs [22]. There are reports of immunocompromised patients having EGWs with high-risk types of HPV [22]. Although current treatments are imperfect, most patients can eventually be wart free. There is no reported resistance of genital HPV currently.

Two new prophylactic HPV vaccines are currently on the market and demonstrate high-level protection (90% or better) from infection, persistent infection and high-grade lesions [21]. One of the vaccines, Gardasil (Merck), protects against HPV types 6, 11, 16, and 18 and the other, Cervarix (GlaxoSmithKline), protects against types 16 and 18 [21].

4 Diseases Characterized by Urethritis and Cervicitis

Urethritis in men and cervicitis in women are among the most common diagnoses in sexually transmitted disease clinics. The majority of cases of urethritis and cervicitis are caused by infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis.* Other agents that cause urethritis are *Trichomonas vaginalis*, *Herpes simplex*, and *Mycoplasma genitalium. Ureaplasma urealyticum* biovar 2 has also recently been linked to urethritis.

4.1 Urethritis

4.1.1 Clinical Description

Urethritis refers to inflammation of the urethra manifested by dysuria, pyuria, or discharge. Discharge may range from scant and mucoid to grossly purulent. It may

occur in males or females, but clinically appears more frequently in men. Although dysuria may suggest a urinary tract infection in females, in males, urethritis is usually due to a sexually transmitted disease (STD).

Per the CDC 2006 STD Treatment Guidelines [1], the criteria for diagnosis of urethritis are the following:

a. Mucopurulent or purulent discharge.
b. A Gram stain of urethral secretions demonstrating greater than or equal to 5 WBCs per oil immersion field. The diagnosis of gonococcal urethritis depends on the demonstration of intracellular Gram-negative diplococci.
c. A positive leukocyte esterase test on a first-void urine or microscopic examination of first-void urine demonstrating greater than or equal to 10 WBCs per high-power field.

Because gonococcal urethritis is so often symptomatic, individuals usually present for diagnosis. In contrast, chlamydial infection is often asymptomatic, even in men. With the advent of highly sensitive and specific non-invasive tests based on nucleic acid amplification (NAATs) (see below) that can be performed using urine in men and a self-administered vaginal swab in women, screening asymptomatic individuals for *Chlamydia* or gonorrhea is feasible in a variety of non-clinical sites.

4.1.2 Epidemiology

Both gonorrhea and *Chlamydia* genital infections are extremely common. In 2006, over 350,000 cases of gonorrhea and 1 million cases of *Chlamydia* were reported to the CDC [23]. However, many cases of both diseases are not reported because of asymptomatic disease and providers' failures to report. The most striking element of chlamydial and gonorrheal epidemiology is their association with young adult age. Both infections are most prevalent in those 15–24 years of age. This association has been linked to anatomic changes, immune responses, and sexual networks. Unlike syphilis, which tends to occur in geographically identified high prevalence areas in the United States, *Chlamydia* and gonorrhea are widespread. Although both occur in advantaged and disadvantaged populations, the latter often bear a disproportionate burden of disease. Similarly, racial differences are prominent. Nationwide, African-Americans, American Indians/Alaskan natives, and Hispanic populations are disproportionately affected by both diseases. There is no biologic reason known for this disparity, and differences are more likely to be due to factors such as access to care and social capital.

4.1.3 Etiology

Neisseria gonorrhoeae

N. gonorrhoeae is a fastidious Gram-negative diplococcus. The organism causes disease by attaching to columnar epithelium via pili, invading mucosa using Opa

(opacity-related proteins), and porins. Porin proteins, Por A and Por B, have been used to serotype gonococci. Opa proteins exhibit a wide range of antigenic variability, which may affect their ability to invade cells.

Chlamydia trachomatis

C. trachomatis is an obligate intracellular pathogen, which makes diagnostic culture techniques more difficult than those for gonorrhea and makes nucleic acid amplified tests a particularly important tool in the diagnosis of infection. Of the three species recognized in the genus *Chlamydia* (i.e., *trachomatis, pneumoniae,* and *psittaci*) only the *trachomatis* species is associated with genital infection. The species is comprised of 19 different serovars that differ in sequence in at least one of their variable regions of the major outer membrane MOMP encoded by the gene omp1. Serovars A, B, Ba, and C are typically associated with trachoma, one of the world's most common causes of reversible blindness. Serovars D, E, F, G, and H are typically associated with urethritis/cervicitis, although L2a, one of the lymphogranuloma venereum serovars (L1, L2a, L2b, and L3), has recently been associated with urethritis. Heat-shock proteins have been studied in relation to the scarring associated with chlamydial infection.

4.1.4 Diagnosis

Nucleic acid amplified tests (NAATs) such as polymerase chain reaction (PCR), ligase chain reaction (LCR), or temperature-mediated amplification (TMA) are the most sensitive diagnostic tests for both gonorrhea and *Chlamydia* and are highly specific. Urine in men and self-administered vaginal swabs in women have high sensitivity and specificity for the detection of *Chlamydia* and gonorrhea. Rates are similar to urethral and cervical swabs. For gonorrhea, culture has the advantage of being inexpensive and it may be used for antibiotic susceptibility testing. Sensitivity of *N. gonorrhoeae* culture, depending on the laboratory and collection conditions, ranges from 65 to 100%. A Gram stain of a urethral discharge typically shows the Gram-negative diplococci associated with neutrophils in $\geq$95% of symptomatic males. Gram-negative diplococci seen extracellularly are considered equivocal. Approximately 50–70% of culture-positive asymptomatic men will have a positive Gram stain. Although Gram stains of endocervical discharge can detect *N. gonorrhoeae*, they are rarely used to diagnose gonorrhea in females because of their low sensitivity.

NAATs offer strong advantages over culture in diagnosing chlamydial infection. First, culture requires highly trained personnel and meticulous technique. Second, even in the best of hands, culture only has sensitivity of 70–80%. Gram stains of the exudate from a patient with *C. trachomatis* infection are non-specific and show only nongonococcal urethritis (NGU), i.e., the presence of neutrophils and *no* intracellular diplococci. In most studies, *C. trachomatis* has been associated with 30–50% of all cases of NGU. It is also found in approximately 20–30% of gonococcal urethritis. No clinical features reliably distinguish chlamydial and nonchlamydial NGU. In

the absence of a positive culture for gonorrhea or *Chlamydia*, NGU is not considered to be caused by either of the two organisms. Evidence to support this belief includes the observation that neither gonorrhea nor *Chlamydia* is isolated from the sexual partners of patients with culture-negative NGU. In addition, individuals with chlamydial NGU respond better to tetracyclines than 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 weeks after treatment. Persistence occurs in less than 20% of those with chlamydial NGU.

4.1.5 Treatment

The CDC's current treatment recommendations for urethritis are shown in Table 6. Although penicillin was the treatment of choice for *N. gonorrhoeae* for three decades the rapid spread of penicillinase-producing *N. gonorrhoeae*, or PPNG, precipitated a need for alternative treatments. The CDC treatment guidelines for gonococcal (GC) infections 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, patients with a positive Gram stain or culture for gonorrhea should be given additional treatment for *C. trachomatis* in the absence of results of testing that specifically exclude it.

Chlamydial genital infection responds well to doxycycline. Single-dose azithromycin has been shown to eradicate *C. trachomatis* and alleviate symptoms. Some practitioners prefer this regimen's use when compliance is in doubt. Erythromycin is also effective, but desirability is limited by its gastrointestinal toxicity. Ampicillin is recommended for 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.

4.1.6 Special Considerations

Partner notification: Treatment of partners should be considered as important as treating the index case of urethritis. All sexual contacts of patients with gonorrhea or chlamydial genital infection in the 60 days prior to the index case's diagnosis should be treated and, if possible, screened for STDs.

Recurrent or persistent urethritis: If non-compliance or re-exposure is unlikely, individuals who remain symptomatic after treatment for NGU should be tested for *Trichomonas* by culture and treated with metronidazole 2 g orally in a single dose plus Azithromycin 1 g [1]. *Trichomonas* testing may also be done using sensitive and specific NAATs.

Disseminated gonorrhea: Disseminated gonorrhea infection (DGI) occurs rarely, in 0.2–1.9% of mucosal cases [24, 25]. The exact mechanism for dissemination is unknown, although it appears to be associated with certain strains and resistance to complement-mediated killing by normal human serum. Patients usually present with an asymptomatic mucosal infection, relatively mild systemic illness,

Table 6 Treatment of urethritis and cervicitis [1, 49]

Treatment of urethritis or cervicitis[a] due to	For *Neisseria gonorrhoeae*	For *Chlamydia trachomatis*
Neisseria gonorrhoeae:	Ceftriaxone 125 mg IM in a single dose *or*	Azithromycin 1 g p.o. in a single dose *or*
Because of a high association of *N. gonorrhoeae* infection with concomitant chlamydial infection, patients with gonorrhea should be treated for *Chlamydia.*	Cefixime 400 mg orally in a single dose or 400 mg by suspension (200 mg/5 ml) *plus* Treatment for C*hlamydia* if chlamydial infection has not been ruled out (see column to the right) Alternative regimens:	Doxycycline 100 mg p.o. b.i.d. for 7 days Alternative regimens: Erythromycin base 500 mg p.o. qid for 7 days *or* Erythromycin ethylsuccinate 800 mg p.o. qd for 7 days, *or* Ofloxacin 300 mg b.i.d. for 7 days
Rectal gonorrhea is treated in the same manner as urethritis with comparable success rates	Spectinomycin[b] 2 g in a single intramuscular (IM) dose *or* Single-dose cephalosporin regimens	If only erythromycin can be used and a patient cannot tolerate the high-dose regimens, the following can be used: Erythromycin base 250 mg p.o. qid for 14 days *or* Erythromycin ethylsuccinate 400 mg p.o. qid for 14 days
For treatment of pharyngeal gonorrhea Pharyngeal gonorrhea is more difficult to treat than urethral, cervical, or rectal gonorrhea. Oral cephalosporins are not recommended for this purpose	Ceftriaxone 125 mg IM *plus* Treatment for *Chlamydia* (see column to the right)	As listed above for treatment of *C. trachomatis*
Chlamydia trachomatis	If Gram stain or culture does not show GC, the patient need only be treated for *C. trachomatis* (see column to the right)	As listed above for treatment of *C. trachomatis*
Nongonococcal urethritis	No treatment required	As listed above for treatment of *C. trachomatis*

[a]These regimens are recommended for all adult and adolescent patients, regardless of travel history or sexual behavior.
[b]Spectinomycin is currently not available in the United States.

asymmetric polyarthralgia, tenosynovitis, and a characteristic skin rash, called the arthritis–dermatitis syndrome. Other patients present with suppurative arthritis and are less likely to have a rash or tenosynovitis. Recommended treatment is ceftriaxone 1 g q 24 h. Cefotaxime and ceftizoxime are alternative treatments. Therapy

should be continued for 10–14 days [1]. Spectinomycin is recommended as an alternative but is not available currently in the United States. Quinolones should not be used unless specific testing demonstrates susceptibility.

4.1.7 Gonorrhea and *Chlamydia* Resistance

Gonorrhea resistance: Isolated reports of penicillinase producing *N. gonorrhoeae* (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.

In 1986, the CDC established a surveillance program, the Gonococcal Isolate Surveillance Project (GISP), to monitor trends in the antimicrobial susceptibility of gonococcal isolates in the United States [26]. The GISP includes 26 publicly funded STD clinics and 5 regional laboratories. At each clinic, urethral isolates are obtained from the first 25–30 men diagnosed with gonorrhea each month. These isolates are shipped to one of the regional laboratories, where the susceptibilities of the organisms to a panel of antibiotics are determined. Worldwide surveillance is performed through the World Health Organization (WHO) via a network of laboratories, entitled the gonococcal antimicrobial-susceptibility program (GASP).

The best known form of beta-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 throughout the Americas and Caribbean has shown a decrease in the incidence of PPNG from about 15% in 1990 to less than 10% in 1995 [27]. Resistance to beta-lactams may also occur through chromosomal mutations. These usually produce low-level penicillin resistance and work through mechanisms other than beta-lactamase production, such as an alteration in the penicillin-binding proteins. Despite decreases in the incidence of PPNG, chromosomal beta-lactam resistance has increased, as has plasmid-mediated high-level resistance to tetracycline [27].

Cases of gonorrhea caused by *N. gonorrhoeae* resistant to fluoroquinolones (QRNG) have increased dramatically in many parts of the world and are becoming widespread in parts of Asia. Quinolone resistance results from point mutations in genes contained in the Quinolone Resistance Determining Region (QRDR). In particular, mutations in the DNA gyrase gene, gyrA, may confer resistance to quinolones, whereas another locus, parC, which specifies a topoisomerase, contributes to quinolone resistance [28]. QRNG strains have increased in the United States and worldwide. Because of this, the CDC has recommended that quinolones not be used in the treatment of gonorrhea unless supported by local epidemiology. In the United States during 1996, less than 0.05% of 4,639 clinical isolates tested from surveillance laboratories had minimum inhibitory concentrations (MICs) > 1.0 μg/ml to ciprofloxacin.

C. trachomatis resistance: Tetracycline-resistant *C. trachomatis* was first described in 1990 [29]. Isolates with this type of resistance formed 100-fold fewer inclusions in the presence of tetracycline than sensitive strains, suggesting that

approximately 1% of the isolates were resistant. Culture of resistant organisms in tetracycline-containing medium yielded populations that were 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. In one study, the tetracycline-resistant isolates were also resistant to doxycycline, erythromycin, sulfamethoxazole, and clindamycin but sensitive to rifampin, ciprofloxacin, and ofloxacin; in a second study, sensitivity to erythromycin and azithromycin was maintained. The significance of resistance in clinical disease remains to be defined.

4.2 Management of Women with Cervicitis

4.2.1 Clinical Description

Cervicitis refers to inflammation of the uterine cervix. The syndrome of mucopurulent cervicitis (MPC) is defined by mucopurulent or purulent discharge and may present to the patient as a vaginal discharge. Diagnosis of MPC is made when a swab, inserted into the cervical os, after swabbing vaginal secretions from the vault, reveals a yellow or green discharge visible on removal. Some but not all investigators consider cervicitis present if the endocervix is friable, that is, it bleeds when a cotton or dacron swab is inserted into the endocervical canal. Women with cervicitis due to gonorrhea or *C. trachomatis* infection may be asymptomatic, experience vaginal discharge, have lower abdominal discomfort, or present with an acute pelvic inflammatory disease (PID) 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. Obstructed fallopian tubes resulting from salpingitis associated with PID may result in ectopic pregnancy.

4.2.2 Epidemiology

The epidemiology of gonorrhea and *C. trachomatis* is similar in men and women except that women tend to be slightly younger than men. *C. trachomatis* infection is common in adolescent girls, often asymptomatic, and commonly recurs. It is recommended that all sexually active female adolescents be screened for *C. trachomatis*. High rates of chlamydial infection are found also in women aged 20–24, particularly those with a new sexual partner.

4.2.3 Etiology

Both gonorrhea 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.

4.2.4 Treatment

The treatment of cervicitis is similar to that of urethritis (see Table 6) [1].

4.2.5 Other Considerations

Sexual partners of women with gonorrhea or *Chlamydia* infection whose last sexual contact was within 60 days before symptom onset should be treated and, if possible, screened to increase case finding [1].

5 Sexually Transmitted Pharyngitis

While *H. simplex* infection and *C. trachomatis* can infrequently cause pharyngitis, sexually transmitted pharyngitis is almost synonymous with gonococcal pharyngitis. Gonococcal pharyngitis is relatively difficult to treat effectively as compared to genital tract infection. Although newer antibiotic regimens are more effective than previous ones, the cure rate for pharyngitis remains less than that for uncomplicated GC genital infection. In a review of clinical trials performed after 1980, more than 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 [30]. For this reason, the recommendations for therapy in pharyngeal gonorrhea do not include oral cefixime, which achieves lower drug levels than ceftriaxone given intramuscularly. The recommended regimen is ceftriaxone. Spectinomycin is an unreliable treatment for gonorrhea pharyngitis [1]. Although not recommended specifically by the CDC, in some areas azithromycin 2 g as a one time dose may be an alternative. With the exception of cefixime, oral cephalosporins such as cefpodoxime have unacceptable failure rates. Quinolones should not be used unless susceptibilities are done or the regional epidemiology suggests susceptibility [1, 31]. Treatment of *C. trachomatis* infection should be initiated with treatment of pharyngeal gonorrhea because of the frequency of co-infection.

6 Sexually Transmitted Proctitis, Proctocolitis, and Enteritis

6.1 Clinical Description

Infection of the gastrointestinal 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 *N. gonorrhoeae*, *C. trachomatis* including lymphogranuloma venereum (LGV) serovars, *H. simplex*, or *T. pallidum* [1].

6.2 Diagnosis

Patients with acute proctitis who practice receptive anal intercourse should be examined with anoscopy to establish a specific diagnosis.

6.3 Treatment

Although proctitis due to *N. gonorrhoeae* responds well to regimens recommended for uncomplicated *N. gonorrhoeae* infection, the recommended treatment if pus is present on examination of the rectum is ceftriaxone 125 mg IM plus doxycycline 100 twice daily for 7 days. Rectal chlamydial infection with the non-LGV serovars responds to the regimens recommended for urethritis. LGV may cause a hemorrhagic proctitis associated with regional lymphadenitis. LGV is treated with doxycycline 100 mg orally twice daily for 21 days or alternatively with erythromycin base 500 mg orally four times daily for 21 days [1].

7 Epididymitis

Both *N. gonorrhoeae* and *C. trachomatis* may ascend the male genital tract to cause 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, more common in adolescents, and often presents with pain that suddenly gets worse. The recommended treatment regimen for epididymitis, like that for proctitis, is ceftriaxone 125 mg IM plus doxycycline 100 mg orally twice daily for 10 days. The recommended alternative regimen is ofloxacin 300 mg orally twice daily for 10 days or levofloxacin 500 mg once daily for 10 days [1].

8 Diseases Characterized by Vaginal Discharge

Abnormal vaginal discharge is one of the leading reasons for visits to primary care physicians in the United States. Symptoms of vaginitis include the following: abnormal discharge, itching, odor, or vaginal pain. Discharge may be mild and colorless, heavy, frothy or curdled, and white, yellow, or grey. This spectrum of presentations adds to the difficulty of diagnosis based solely on observation. Therefore, clinical diagnosis is based on a variety of components including observed signs, simple clinical tests, and potentially laboratory-based testing. Differential diagnosis may include physiologic discharge, chemical or irritant vaginitis, atrophic vaginitis, or vaginitis due to infectious agents. The three most common infectious causes of vaginitis are bacterial vaginosis, *Candida albicans* (the causative agent of yeast infections), and *T. vaginalis* (the causative agent of trichomoniasis) [32, 33].

Patients should undergo a speculum exam with careful examination of the cervix for discharge and to collect diagnostic swab samples. In the absence of cervical discharge, the vaginal mucosa should be examined and sampled as well. Tests that can readily be performed in the physician's office include measurement of pH and wet preparation microscopy using both normal saline and potassium hydroxide (KOH) solutions. Samples also may be referred to a centralized laboratory for *C. trachomatis* and *N. gonorrhoeae* testing, Gram's stain, culture for yeast or *T. vaginalis*, or DNA-based testing for *T. vaginalis*.

8.1 Bacterial Vaginosis

8.1.1 Clinical Description

Bacterial vaginosis (BV) is a syndrome with unclear etiology that results when the balance of the normal flora in the vaginal micro-environment is disrupted. Rather than a true infectious disease, BV is more likely the result of changes to the flora in response to a disruptive event. The largest change is generally a reduction of *Lactobacillus* spp., in the vagina, which results in a pH change. These two events then create a more permissive environment for bacteria such as *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Prevotella* spp., and anaerobes such as *Bacteroides* spp. Recent studies using DNA-based techniques suggest that *megasphaera* phylotype and an as-yet unidentified bacterium are frequently present in women with BV [34].

8.1.2 Etiology

The lack of a distinct etiology hinders our understanding of the transmission mechanisms for this disease. Transmission is associated with sexual activity in some cases but can occur in women with no history of sexual behaviors. Sexual activity is a risk factor for this disease (higher rates of disease are found in sexually active women), as is having multiple sex partners or acquisition of a new partner. However, using an intrauterine deviceand douching, which are not related to sexual behaviors, are also risk factors, thus supporting the theory that BV results from activities that are disruptive to the vaginal environment. From this perspective, sexual activity may be a risk factor as a result of the disruption of both the pH and the vaginal mucosa that occur as part of sexual activity rather than the transmission of a specific organism. In all likelihood, a combination of events (infectious, chemical, and/or mechanical) is responsible for BV, explaining the wide variation in presentation of the disease.

8.1.3 Diagnosis

BV is characterized by fishy-smelling, homogenous, white discharge that adheres to the vaginal mucosa. Vulvovaginal itching and burning and pain during coitus are commonly associated with BV. Clinical diagnosis is based on a set of observations called Amsel's criteria [35]. The presence of at least three of the following criteria is indicative of BV: (1) homogenous, adherent discharge with little evidence of inflammation; (2) vaginal pH > 4.5; (3) amine (fishy) odor after addition of 10% KOH solution to wet prep vaginal fluid; and (4) presence of bacteria-coated epithelial cells (clue cells) seen on wet prep microscopy. Improved specificity of diagnosis can be achieved with use of Gram's stain of a vaginal smear. Criteria for a diagnosis of BV using Nugent's scoring [36] include 0–4 points for the lack of lactobacilli morphotypes (higher score when fewer are present); 0–4 points for gardnerella/bacteroides morphotypes (higher score when more are present); and 0–2 points for the presence

of curved, Gram-variable rods (higher score when more are present). A total score of >7 is diagnostic for BV.

8.1.4 Treatment

Consequences of untreated BV can be quite serious. In pregnant women, BV has been associated with adverse outcomes such as preterm labor, preterm delivery, premature rupture of membranes, and chorioamnionitis. Pelvic inflammatory disease and endometritis are also associated with BV. Finally, BV has been strongly implicated as increasing risk of acquisition of HIV [37, 38].

Table 7 summarizes the various therapies recommended by the CDC for BV. Oral and intravaginal forms of metronidazole and clindamycin are the cornerstones to therapy for BV. There are minimal differences between the two drugs in regard to efficacy, so choice may be guided by differences in cost, mode of administration, and adverse effects [39]. Antimicrobial testing of anerobic Gram-negative rods recovered from women treated for BV may reveal an increase in clindamycin-resistant organisms. After treatment of BV, recurrence may occur in up to 30% of women within 3 months [39]. A newer BV treatment, tinidazole, is a nitroimidazole-like metronidazole. In a recent trial, tinidazole 1 g daily for 5 days and 2 g daily for 2 days were significantly superior to placebo [40].

8.2 Trichomoniasis

T. vaginalis in women has been found in different genitourinary sites: vagina, urethra, Bartholin's and Skene's glands, and endocervix. Presentation in women can vary from asymptomatic to severe vaginitis with vaginal discharge, pruritus, dysuria, and abdominal pain. In men, the organism has been isolated from the urethra, urine, semen, external genitalia, epididymitis, and prostate. Men with *T. vaginalis* infection can be asymptomatic or complain of urethral discharge or dysuria. Unfortunately, men are not routinely screened or treated for this infection and as a consequence there is a lack of information about the disease in men.

8.2.1 Etiology and Epidemiology

Trichomoniasis is caused by the parasitic protozoan *T. vaginalis.* This motile organism is associated with the squamous epithelial cells of the vagina. *T. vaginalis* is the most prevalent non-viral STI both globally and within the United States. The estimated number of cases occurring annually is 170 million worldwide and 5 million in the United States alone [41]. The infection is more often identified in women but is transmitted sexually. Men appear to carry the organism but do not frequently develop overt disease. Interestingly, the prevalence of *T. vaginalis* increases with age, peaking in women 40–45 years old. In settings with high risk for other sexually transmitted infections, the prevalence of *T. vaginalis* in adult

Table 7 Treatment of vaginitis [1]

Vaginitis	Drug	Dose	Duration	Comments
Bacterial	Metronidazole	500 mg p.o. b.i.d.	7 days	51
	Metronidazole vaginal gel 0.75%	5 g b.i.d.	5 days	
	Clindamycin vaginal cream 2%	5 g qhs	7 days	
Alternative	Lindamycin	300 mg p.o. b.i.d.	7 days	
Pregnancy	Clindamycin ovules	100 mg intravaginal qhs	3 days	Due to concerns of increased adverse events (low birthweight and neonatal infections), intravaginal clindamycin cream should only be used during the first half of pregnancy
	Metronidazole	500 mg p.o. b.i.d.	7 days	
	Metronidazole	250 mg p.o. t.i.d.	7 days	
	Clindamycin	300 mg p.o. b.i.d.	7 days	
T. vaginalis	Metronidazole	2 g p.o.	1×	
Alternative	Tinidazole	2 g p.o.	1×	
	Metronidazole	500 mg p.o. b.i.d.	7 days	
Candidiasis	Fluconazole	150 mg p.o.	1×	
	Intravaginal creams			
	Butoconazole 2%	5 g qhs	3 days	

(Continued)

Table 7 (continued)

Vaginitis	Drug	Dose	Duration	Comments
	Butoconazole 2% sustained release	5 g qhs	1×	
	Clotrimazole 1%	5 g qhs	7–14 days	
	Miconazole 2%	5 g qhs	7 days	
	Terconazole 0.8%	5 g qd	3 days	
	Terconazole 0.4%	5 g qd	7 days	
	Vaginal suppositories			
	Miconazole	100 mg qd	7 days	
	Miconazole	200 mg qd	3 days	
	Miconazole	1,200 mg qd	1 day	
	Terconazole	80 mg qd	3 days	
	Nystatin	100,000 u qhs	7 days	
Recurrent VVC	Clotrimazole	100 mg qd	7 days	
	Clotrimazol	100 mg 2 tablets qd	3 days	
	Clotrimazol	500 mg	1×	
	Ointment	5 g	1×	
	Tioconazole 6.5%			
	Induction		14 days	Continue until patient is asymptomatic and cultures are negative
	Choose one of the above for induction for 7–14 days then start maintenance			

women is often equal to the prevalence of *C. trachomatis* and *N. gonorrhoeae* combined.

8.2.2 Diagnosis

A common misconception is that the majority of women with *T. vaginalis* infection are symptomatic. This is an artifact of the definition of trichomoniasis that includes the description of fulminate frothy discharge and often punctuate micro-abrasions of the ectocervix ("strawberry cervix"). In studies using DNA-based diagnostic methods, over 40% of women with *T. vaginalis* had no clinical symptoms of infection [42]. Another factor that leads to the misconception of exclusively symptomatic disease is that the majority of cases are diagnosed based on wet prep microscopy. Unfortunately, in many cases, the organism load is insufficient for capture in the sample used for wet prep. This occurs in part because as samples await microscopic examination, in as few as 10 min at room temperature, the organisms lose motility, a requirement for a diagnosis of trichomoniasis. Therefore, the cases diagnosed by this method have higher organism burden, which frequently leads to a higher probability of symptoms. Wet prep microscopy has been shown to be less sensitive than culture, which itself is less sensitive than DNA-based testing. In many settings, wet prep microscopy is only 50–70% sensitive, thus many cases of *T. vaginalis* infection are undiagnosed. There are commercially available rapid diagnostic tests (The Affirm VP III, OSOM Trichomonas Rapid Test, and Xenostrip) which appear to be as good as or slightly better than wet prep microscopy.

For many years, infection with *T. vaginalis* has been considered to be merely a nuisance. However, data are now available that suggest that *T. vaginalis* is associated with PID and adverse outcomes of pregnancy. In addition, longitudinal data demonstrate that infection with *T. vaginalis* increases the risk of HIV acquisition within the next 3 months by 2.7-fold even when other behavioral risk factors are taken into account [43]. Given the high prevalence of this disease, particularly in populations at risk for HIV infection, it is clear that the use of more sensitive diagnostic tests is warranted.

8.2.3 Treatment

The effective treatment of trichomoniais in the United States has relied solely on the use of metronidazole until the recent FDA approval of tinidazole (see Table 7). Currently, cost more than efficacy favors metronidazole for the treatment of *T. vaginalis* infections. Clinical resistance to metronidazole has been reported since 1962 [44]. Antibiotic susceptibility testing for *T. vaginalis* is not standardized. Metronidazole doses as high as 1 g three times daily coupled with intravaginal metronidazole have been successfully used for refractory cases. However, side effects (nausea, vomiting, etc.) of metronidazole may be prohibitive [44]. In one study, patients with refractory trichomoniasis were treated successfully with high doses of tinidazole (2–3 g orally plus 1–1.5 g intravaginally for 14 days) [45]. There is cross-reactivity between metronidazole and tinidazole, and, as there are

no effective alternatives, desensitization followed by treatment is recommended for metronidazole-allergic patients.

8.3 Vulvovaginal Candidiasis

8.3.1 Clinical Description

Vulvovaginal candidiasis (VVC) typically presents with acute pruritus and vaginal discharge. VVC is frequently accompanied by vulvar pruritus as well as dysuria, dysparenuria, and vaginal burning. Symptoms can be exacerbated in the week preceding the onset of menstrual flow.

8.3.2 Etiology and Epidemiology

VVC is predominately caused by *C. albicans* or *Candida glabrata*. These fungi are normal flora of the gut and urogenital tract, associated with mucosal surfaces. Similar to BV, yeast "infection" is often a result of a disturbance of the environmental balance that results in yeast proliferation.

It is estimated that 75% of women will have at least one episode of VVC in their lifetimes. Risk factors for developing VVC include pregnancy, diabetes mellitus, recent use of antibiotics, and corticosteroid use. VVC is not a sexually transmitted infection. The incidence of VVC increases with age, peaking in the fourth and fifth decade of life. Sporadic VVC usually occurs without an obvious precipitating factor, with the exception of uncontrolled diabetes. There may be a relationship between VVC and HIV [37], but further research into this area is needed.

8.3.3 Diagnosis

Speculum examination and collection of samples is required for clinical diagnosis. Diagnosis is based on the presence of a thick, white adherent discharge that, unlike the case with BV, is not homogeneous, but rather has a clumpy, or "cottage cheese-like," appearance. VVC is associated with vulvar itching, vaginal burning, and pain on urination and/or coitus. Wet preparations for microscopy, as with all vaginitis, should be prepared using both normal saline and 10% KOH solutions. Microscopy will reveal yeast and pseudohyphae. The pH is typically <4.5, and higher values may be indicative of mixed infections. Culture for yeast is available from reference laboratories and is recommended when signs indicate infection but no yeast or pseudohyphae are observed microscopically. Additionally, the diagnosis of recurrent VVC should be confirmed by culture. VVC due to azole-resistant strains of *C. albicans* is rare [45]. Most clinically resistant VVC appears to be with non-*albicans* species, particularly with *C. glabrata*.

In addition to uncomplicated VVC, more severe cases can occur. These cases require prolonged antifungal therapy. Factors related to risk of complicated candidiasis include uncontrolled diabetes, immunosuppression, history of recurrent candidiasis, and recent antibiotic use.

8.3.4 Treatment

Patient preference should influence the choice of treatment for 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 (see Table 7). Oral systemic azole agents achieve comparable therapeutic cure rates; however, only fluconazole is recommended by the CDC at this time [1]. Fewer than 5% of women experience severe or recurrent VVC, defined as ≥4 episodes per year. In contrast to complicated infection, these cases are infrequently associated with uncontrolled diabetes or immunosuppression. In recurrent cases, a more rigorous laboratory work-up and history is required prior to initiation of therapy. These patients should receive induction therapy (14-day course of an agent in Table 7) to achieve negative vaginal cultures and then a maintenance regimen should be instituted for 6 months [1].

Little information regarding optimal treatment of *C. glabrata* vaginal infection is available. *C. glabrata* isolates have intrinsic reduced susceptibility to azoles. Boric acid 600 mg gelatin capsule administered vaginally once daily for 14 days has been shown to be moderately effective [1, 46].

9 Pelvic Inflammatory Disease

9.1 Clinical Description

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. The majority of women have complete recovery; however, long-term sequelae of PID can be severe and include ectopic pregnancy, infertility, and chronic pelvic pain. 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.

9.2 Diagnosis

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 [1].

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 [1]. 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 [1].

C. trachomatis and *N. gonorrhoeae* are well-documented causes of PID. A randomized, controlled trial found that identifying and treating women with chlamydial cervical infections reduced the incidence of PID [47]. PID is frequently a polymicrobial infection with bacteria such as *M. hominis, H. influenzae, G. vaginalis, Staphylococci, Group B Streptococci, E. coli,* and anaerobes. 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 [47]. Microbial species associated with BV are often recovered from upper genital tract or cul-de-sac specimens of women with acute PID.

9.3 Treatment

Given the serious consequences of PID, prevention and early treatment should be a priority. The CDC recommends hospitalization for patients who are pregnant, noncompliant, failing outpatient regimens, or not tolerating oral antibiotics; who have severe symptoms (nausea, vomiting, or high fever) or have a TOA; and in whom a surgical emergency cannot be excluded [1]. Table 8 lists the CDC's treatment recommendations for PID. All patients, whether treated on an inpatient or outpatient basis, should have follow-up within 3 days of initiation of therapy. If no improvement is noted despite 72 h of appropriate treatment, then additional testing, other diagnoses, or surgical referral should be considered [1]. Some recommend rescreening for *C. trachomatis* and *N. gonorrhoeae* 4–6 weeks after completion therapy. Evaluation of male sexual partners of patients with PID is an essential component of treatment.

10 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 sexually transmitted [1]. 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 the absorption, and also not be prescribed for persons with extensive dermatitis or for pregnant women or children <2 years of age [1].

Table 8 Treatment of PID [1, 49]

Type of treatment	Duration
Parenteral	
Regimen A 2 g cefotetan intravenously (i.v.) q 12 h *or* 2 g cefoxitin i.v. q 6 h *plus* 100 mg doxycycline p.o. or i.v. q 12 h	Continue for at least 48 h after the occurrence of significant clinical improvement; Doxycycline should then be given orally for a total of 14 days
Regimen B 900 mg clindamycin i.v. q 8 h *plus* Gentamicin 2 mg/kg IV/IM loading dose then 1.5 mg/kg q 8 (can substitute with single-dose gentamicin)	Continue for at least 48 h after clinical improvement. Doxycycline 100 mg (as above) or Clindamycin, 450 mg orally 4 × a day should be given until day 14 of treatment
Alternative 3 g ampicillin/sulbactam i.v. q 6 h *plus* Doxycycline (as above)	Same principles as above
Oral	
Regimen A Ceftriaxone 250 mg IM in a single dose *plus* Doxycycline 100 mg p.o. b.i.d. with or without metronidazole 500 mg p.o. b.i.d.	Continue both for 14 days
or Other parenteral third-generation cephalosporin (ceftizoxime or cefotaxime) *plus* Doxycycline 100 mg p.o. b.i.d. with or without metronidazole as above	Continue for 14 days
Alternative Oral Regimens	
If parenteral cephalosporin therapy is not feasible, then use of fluoroquinolones (levofloxacin 500 mg qd for 14 days) with or without metronidazole as above may be considered if the community prevalence and individual risk of gonorrhea is low. Tests for gonorrhea must be performed. If the test is positive, parenteral cephalosporin is recommended or treatment directed toward antimicrobial susceptibilities of the isolate if cultures were performed [49]	

10.1 Pediculosis Pubis

Crab lice may infest the pubic and perianal areas and can extend to the beard, axilla, and eyelashes (phthiriasis palpebrarum). The CDC recommends 1% permethrin cream or pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 min [1]. Treatment should be applied to all hairy areas of the body. Due to reported increases in resistance to pediculicides, malathion may be used when treatment failures are suspected. Ivermectin 250 μg/kg repeated in 2 weeks is also recommended as an alternative regimen [1]. Lindane is no longer recommended as first-line therapy because of increased toxicity (seizure and aplastic anemia) [1]. Cure rates of 60% have been reported for single treatment with 1% permethrin [48]. Reportedly, a second treatment 1 week later will increase the cure rate to 72%, and a 93% cure rate is achieved with a single treatment of 5% permethrin [48].

10.2 Scabies

The CDC recommends 5% permethrin cream (wash off 8–14 h later) or ivermectin 200 μg/kg orally, repeated in 2 weeks for the treatment of scabies. An alternative regimen is 1 oz of 1% lindane (wash off in 8 h) [1]. Patients, especially those who are HIV positive, can develop crusted scabies (Norwegian scabies). Recommended treatment is with 200 μg/kg of ivermectin as a single dose in immunocompetent patients and two doses in immunocompromised patients [48]. Some experts recommend ivermectin on days 1, 15, and 29 [1].

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 [48]. Lindane resistance in scabies has been reported in the United States, and lindane resistance is reported as “commonplace” in Peru [48]. 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.

11 Other Considerations

Hepatitis A and hepatitis 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 [4].

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.
- Fluoroquinolones are no longer recommended in gonococcal infections due to increasing resistance.
- The emergence of resistance has impacted the recommended management of sexually transmitted ectoparasitic infections.

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Gastrointestinal Tract Infections

Robert E. Post and Barry L. Hainer

1 Introduction

Gastrointestinal (GI) tract infections are caused by a wide variety of fungi, viruses, and bacteria, and all areas of the GI tract are affected. Infections range from mild, where disease is self-limited and supportive care is the treatment, to severe, where hospitalization and intravenous fluids and antibiotics are required for survival. In recent years, the increasing antibiotic resistance of various bacteria has become an important aspect of GI infection treatment and has resulted in augmentation of therapy.

2 Oral and Esophageal Infections

2.1 Fungal Infections

2.1.1 Overview

Humans are constantly exposed to fungi in their daily activities, especially while eating. Among human yeast isolates, *Candida albicans* is the most prevalent and the most common cause of oropharyngeal and esophageal fungal infections. When isolated from the oral cavity, *Candida* can be found in 31–60% of healthy people [1]. Candidiasis is a common infection, especially in those who are immunocompromised [2]. Over the past several decades, the prevalence of these infections has increased; this is most likely due to the increased number of patients with HIV/AIDS, cancer patients, and transplant patients [3]. In some patients, candidiasis of the oral mucosa may be the first sign of infection with HIV. In those with more advanced HIV, esophageal candidiasis is as common as oropharyngeal candidiasis [4]. Factors that contribute to a predisposition to develop candidiasis

R.E. Post (✉)
Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: postr@musc.edu

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include age (infants and the elderly), HIV infection, diabetes mellitus, use of H2 blockers, mucositis (chemotherapy induced), radiation, dentures, trauma, surgery, or malignancy. Humans are repeatedly exposed to Candida in food and other sources, including the hospital environment, and personnel [3].

2.1.2 Clinical Presentation

Thrush or oral candidiasis can present in a variety of ways; these include incidental findings in asymptomatic patients or complaints of a burning tongue, dysphagia, and a painful mouth. Clinically, thrush presents as diffuse erythema with white plaques on the surfaces of the oropharyngeal mucosa. These plaques can be wiped away to reveal a raw, erythematous, and sometimes bleeding base [3].

Candidal esophagitis most commonly presents with dysphagia, odynophagia, and retrosternal pain. Sometimes, AIDS patients present with fever or epigastric pain or they may be asymptomatic. Proof of diagnosis can only be made by biopsy of esophageal plaques. Biopsies are taken during endoscopy, and the typical appearance is yellow-white plaques on an erythematous background [3].

2.1.3 Treatment

Nystatin is generally an effective treatment for oral candidiasis, but compliance and tolerance can be a problem in immunocompromised patients where this fungistatic antifungal is less effective and requires lengthy therapy. For HIV-positive patients, the azole class of antifungals has replaced nystatin as the treatment of choice. Clotrimazole, 10 mg troches administered five times daily, has been shown to be effective for mild to moderate cases. Ketoconazole, 200 mg daily for 10–14 days, has been shown to treat greater than 80% of cases. Ketoconazole is highly effective even in patients with malignancy or HIV/AIDS. Treatment with ketoconazole has been limited by concerns for hepatotoxicity and reliability of gastric absorption. Fluconazole, 50–100 mg daily, has also been shown to have a cure rate of approximately 80%. Fifty milligrams daily of fluconazole for 10 days and 200 mg daily for 5 days have been shown to cure AIDS-related thrush. AIDS patients are at high risk for symptomatic recurrences. Fluconazole, 100 mg daily, has also been shown to be effective for prophylaxis of thrush in AIDS patients. Itraconazole, 100–200 mg daily, has been shown to be as effective as fluconazole for acute treatment [3].

Oral or intravenous fluconazole is the drug of choice for treatment of candidal esophagitis. In several studies, oral itraconazole has shown similar clinical response rates to fluconazole, with both treatments being well tolerated. Intravenous amphotericin B can be used for azole-refractory cases. Low-dose amphotericin B, 0.3–0.5 mg/kg daily for 10 days, is usually effective for moderate disease [3].

With increasing resistance of fluconazole, drugs from the echinocandin class, specifically micafungin and anidulafungin, have been increasingly studied for treatment of candidiasis. In one study, micafungin was shown to have similar efficacy to fluconazole with HIV-positive patients [2]. In another recent study, anidulafungin was found to have statistically similar efficacy to fluconazole; however, the relapse

rate at a 2-week follow-up was significantly higher for the anidulafungin group [4]. Some studies have also shown that use of echinocandins has bred cross-resistance to other drugs in this class. Fluconazole remains the first-line treatment for candida esophagitis [2].

3 Gastric Infections

3.1 Helicobacter pylori

3.1.1 Overview

Helicobacter pylori is one of the main causes of chronic peptic ulcer disease. It is also the main cause of chronic gastritis and the development of gastric cancer, which is responsible for 1 million deaths worldwide each year. There have been conflicting study results as to whether this bacteria is also linked with GERD and hyperemesis gravidarum [5, 6]. This bacteria is found in 48% of patients with peptic ulcer disease; in developing countries, it is found in 80% of middle-aged adults [5, 7]. In the United States, African-Americans, Hispanics, and older adults have a higher prevalence than the general population. Increased prevalence of *H. pylori* infection is usually correlated with lower income and lower education levels [5].

3.1.2 Clinical Presentation

Clinically, patients with peptic ulcer disease generally have the following symptoms: gnawing or burning epigastric pain that occurs 2–5 h after meals or on an empty stomach and nighttime pain that is relieved by food intake, antacids, or antisecretory agents (such as H2 blockers or proton pump inhibitors (PPI's)). Other possible symptoms include indigestion, vomiting, anorexia, intolerance of fatty foods, and heartburn. There is more likely to be a positive family history of *H. pylori* infection in these patients. Physical examination is an unreliable tool in making the diagnosis. The ELISA serum antigen test is a useful tool to test for initial infection with a sensitivity of 85% and a specificity of 79%. However, it cannot be used to test for eradication of the bacteria. The urea breath test has a higher sensitivity and specificity (95–100% and 91–98%, respectively) and can be used to confirm eradication; however, a patient needs to have stopped PPI therapy 2 weeks prior to the test for results to be reliable. The most direct diagnostic test is an endoscopic biopsy, which has a sensitivity greater than 95% and a specificity of 100%. This success in diagnosis has to be weighed with the invasive nature and expense associated with upper gastroesophageal endoscopy [7].

3.1.3 Etiology

Patients are usually exposed to and infected by *H. pylori* as children and retain the infection throughout life unless treated. The mode of transmission in unknown

at this time, but current theories suggest oral–oral, fecal–oral, maternal–infant, conjugal, or iatrogenic routes. In countries where *H. pylori* prevalence is greater than 50%, there are some data suggesting that having a partner infected with *H. pylori* increases risk of infection by six times. The overall prevalence of peptic ulcer disease has been declining in developed countries for many decades, in part due to improved sanitation, but also due to increased antibiotic treatment of *H. pylori* [5].

H. pylori infection creates an environment in the gastric mucosa that favors ulcer formation and these include the following: increased resting and meal-stimulated gastrin levels, decreased gastric mucus production, and decreased duodenal mucosal bicarbonate secretion. The key to reducing ulcer reoccurrence is to eliminate the *H. pylori* [7]. Patients with *H. pylori* infection and duodenal ulcers have a gastric acid secreting rate three times higher than those who are not infected. Some patients infected with *H. pylori* have lower than normal rates of gastric acid secretion, and it is in these patients that gastric ulcers are more common [5]. Treatment has been shown to reduce duodenal ulcer reoccurrence from 67 to 6% and gastric ulcer reoccurrence from 59 to 4% [7].

3.1.4 Treatment

Treatment of *H. pylori* is vital in successful treatment of peptic ulcer disease. It is well known that eradication of the bacteria hastens the healing of ulcers and prevents relapses and complications [5]. Treatments should be administered for 7–14 days and have a success rate of 80–90% [7, 8]. Recommended treatment regimens can be found in Table 1.

The triple therapy regimen (option number 1 in Table 1) is the most common treatment used. However, a fall in the *H. pylori* eradication rate has been observed over the last few years due to increased clarithromycin resistance, and thus new treatment regimens are being proposed. One such European-based regimen, known

Table 1 Treatment regimens for *Helicobacter pylori* infection

1. Proton pump inhibitor (omeprazole 20 mg twice daily or lansoprazole 30 mg twice daily)
and amoxicillin 1 g twice daily or Flagyl 500 mg twice daily
and clarithromycin 500 mg twice daily
2. Ranitidine bismuth citrate (not available in the United States) 400 mg twice daily
and clarithromycin 500 mg twice daily or metronidazole 500 mg twice daily
and tetracycline 500 mg twice daily or amoxicillin 1 g twice daily
3. Pantoprazole 40 mg twice daily
and levofloxacin 500 mg daily
and amoxicillin 1 g twice daily
4. Bismuth subsalicylate 525 mg four times daily
and metronidazole 250 mg four times daily
and tetracycline 500 mg four times daily
and an H2 blocker for 28 days or a proton pump inhibitor for 14 days

Information obtained from [7]

as the sequential therapy regimen, is becoming more widely studied. This regimen includes a PPI twice daily and amoxicillin 1 g twice daily for 5 days followed by a twice-daily regimen of a PPI, clarithromycin 500 mg, and tinidazole for five more days. Early results are promising, with a treatment success rate of over 90% [9].

Another area of recent study is the use of probiotics in the treatment of *H. pylori* [10]. Probiotics are bacteria that aid the host in improving immunity and the nutritional and microbial balance in the gastrointestinal tract. Most probiotics sold today are a group known as the lactic acid bacteria. These include the lactobacillus, streptococcus, and bifidobacteria species, which are all normal and beneficial residents of the human gastrointestinal tract [11]. Animal studies have shown that probiotics reduce the gastric inflammation associated with *H. pylori* infection. Lactobacilli has been shown, in vitro, to reduce the growth of *H. pylori* and inhibit adhesion to the gastric mucosa [11]. The majority of human studies have shown improvement in eradication when probiotics were added to the conventional treatment regimens. However, no studies have demonstrated definitive *H. pylori* eradication with probiotics on their own [10, 11].

4 Intestinal Infections

4.1 Viral Infections

4.1.1 Rotavirus

During childhood, rotaviruses are the most common cause of severe gastroenteritis, and, by the age of 5 years, most children will be infected by them. In children younger than 5 years, they cause 114 million cases of diarrhea each year worldwide. Six hundred thousand of these children die each year, and 98% of these deaths occur in developing countries. Infection with *rotavirus* can help confer future immunity. Forty percent of children with one infection are protected against further infections, 75% are protected against further diarrhea, and 88% are protected against future severe disease. The goal of the oral *rotavirus* vaccines is to try to duplicate this immunity. RotaTeq is the vaccine currently available in the United States. It is composed of human–bovine pentavalent strains to induce immunity to the most common antigenic types, P[8]G1–G4, which account for approximately 90% of strains worldwide. This vaccine is given in three doses, the first at 6–12 weeks of age, and the second and third doses at 4–10 week intervals to complete the three total doses by 32 weeks of age. It is indicated for preterm infants, since they are at the greatest risk for *rotavirus* infection [12]. The Rotavirus Efficacy and Safety Trial (REST) showed this vaccine to decrease gastroenteritis hospital admission by 59%. Overall, it prevents severe *rotavirus* gastroenteritis by 90–95%. Unlike older *rotavirus* vaccines, RotaTeq was not found to be associated with increased risk of intussusception [13]. An additional *rotavirus* vaccine, Rotarix, is pending review by the Food and Drug Administration (FDA).

4.1.2 Norovirus

Human noroviruses are the number one cause of non-bacterial gastroenteritis outbreaks in the world. In the United States alone, there are over 23 million infections per year. *Norovirus* infections should not be taken lightly; they can cause hospitalization in children and deaths in nursing home outbreaks. Since 2002, outbreaks of noroviruses on cruise ships have been well publicized in the media. Kaplan et al. have developed criteria for the identification of noroviruses as the cause of non-bacterial gastroenteritis outbreaks. These include a stool culture that is negative for bacteria, vomiting in over half of cases identified, a mean (or median) incubation period of 24–48 h, and a mean (or median) illness duration of 12–60 h. These criteria carry a sensitivity of 68% and a specificity of 99%. Transmission of *norovirus* can occur by person to person, fecal–oral, contaminated food and water, and aerosolization of vomitus [14]. There is no specific therapy for *norovirus* infection. Treatment is supportive by maintaining hydration and correcting electrolyte disturbances through oral and intravenous hydration [15].

5 Acute Infectious Diarrhea

5.1 Overview

Diarrhea is a common problem. Worldwide, over 2 million deaths each year can be attributed to diarrhea. In the United States, between 211 and 375 million episodes of acute diarrhea occur each year, with almost 1 million hospitalizations and 6,000 deaths each year [16]. Acute diarrhea is defined as bowel movements at least three times per day or at least 200 g of stool per day for less than 14 days [16, 17]. Three diarrhea-free days intervening in a stretch of a diarrhea constitutes a new acute episode [18]. Most cases of diarrhea are viral and self-limited, about 50% last less than 24 h [16]. About 10% of diarrhea cases can be attributed to bacterial pathogens in developed countries [19]. Most episodes of diarrhea in the United States occur in the winter months and are caused by noroviruses and rotaviruses, which have been explained in detail earlier in this chapter [16].

5.2 Clinical Presentation

Diagnosis can mainly be made through history. The elapsed time when symptoms started, after the ingestion of possibly contaminated food, can be a clue to diagnosis as well as what particular foods a patient ate. A past medical history, including possible compromised immunity, antibiotic history, travel, and sexual orientation are all important pieces of information for narrowing a differential diagnosis. The main goal of the physical examination is to assess the degree of dehydration. Laboratory studies are generally unreliable. Stool cultures are widely used, but the blanket use of them has made them expensive, with the cost per positive result ranging from $900 to $1,000 [18].

5.3 Treatment

The initial therapy for all cases of diarrhea is rehydration. Oral rehydration treatment (ORT), which includes fluids with glucose and sodium, is preferred. This is because sodium absorption increases when coupled with glucose, and water absorption increases with sodium [16, 17, 19]. Adults in developed countries are encouraged to drink fluids and eat soup or salted crackers. Another common treatment is the combination of the "BRAT" diet, consisting of bananas, rice, applesauce, and toast, with the avoidance of dairy. Loperamide, an agent that inhibits peristalsis in the gut, has been shown to reduce the duration of diarrhea by up to 24 h in adults [16]. However, it should be avoided in patients with bloody diarrhea or febrile disease where it can possibly prolong the duration of disease [16, 18]. It should also be avoided in children [18]. Bismuth subsalicylate has been shown to reduce the duration of norovirus-associated diarrhea in children by 20–27 h [16]. It has also been shown to increase sodium and water reabsorption in the gut, bind enterotoxins, and has a direct antibacterial effect [17].

6 Traveler's Diarrhea

6.1 Overview

Acute diarrhea is the most common illness among travelers, occurring in up to 55% of people who travel from developed countries to developing countries, including 46% of Americans. Most cases develop within the first 14 days of travel and can last up to 4 days without treatment [20].

6.2 Clinical Presentation

Traveler's diarrhea (TD) is defined as three or more uncomfortable, unformed stools in 24 h with at least one of the following symptoms: fever, nausea, vomiting, abdominal cramps, tenesmus, or bloody stools [20, 21]. TD is more common in children than in adults, and they are at higher risk for dehydration. Parents should seek immediate treatment for their child if he or she has signs of at least moderate dehydration, bloody diarrhea, fever higher than 102°F, or intractable vomiting. Young children can normally have three or more loose stools daily, so diarrhea in this age group is defined as double the frequency of unformed stool [20].

6.3 Etiology

Regions where the risk of acquiring TD are highest include Africa, South Asia, Latin America, and the Middle East. Other risk factors include an immunocompromised state and patients taking H2 blockers or proton pump inhibitors. The main mode of

transmission is fecal–oral; contaminated food and water are the main reservoirs of infectious organisms. Unsafe foods include raw vegetables, unpeeled fruits, raw or poorly cooked meats and seafood, unpasteurized dairy products, cold sauces, salsas, foods that are cooked and then reheated, and tap water. *Escherichia coli* (especially in Mexico, Latin America, the Caribbean, and Africa), *Campylobacter* (especially in Thailand and Nepal), *Shigella*, and non-typhoid *Salmonella* are all common pathogens (to be discussed in more detail later in this chapter). Viruses are not common causes, but noroviruses have been responsible for outbreaks on cruise ships [20]. In 20–50% of cases, no offending pathogen is identified [21].

6.4 Treatment

The best treatment is prevention. The most common travel advice is to boil, cook, or peel the foods and beverages they are about to consume [20]. Even with this advice, the incidence of TD has not decreased in the last 50 years. In fact, most studies do not support a link between personal hygiene and preventing TD. This is likely due to the fact that most travelers eat their meals at restaurants, which have been found to be an independent risk factor for developing TD [21]. Antibiotic prophylaxis is not routinely recommended, despite fluoroquinolones being up to 90% effective [20, 21]. This practice is due to concern for increased bacterial resistance and travelers developing a false sense of security [20]. Bismuth subsalicylate is up to 62% effective in preventing TD [21]. However, it should be avoided in patients taking doxycycline for malaria prophylaxis because it interferes with its absorption [20]. Pregnant women and those taking anticoagulants should also avoid subsalicylates. Probiotics such as *Lactobacillus* have shown 15–63% effectiveness for prophylaxis [20, 21].

Empiric antibiotic treatment should be started within the first 24 h of symptoms. Fluoroquinolones, particularly ciprofloxacin (500 mg twice daily orally for 1–3 days), have been the drug of choice for empiric TD treatment [20]. However, *Campylobacter* resistance to fluoroquinolones has been on the rise, particularly in Thailand, where it increased from 0% in 1987 to 96% in 1997 [21]. In places where fluoroquinolone-resistant *Campylobacter* is prevalent, azithromycin, 500 mg daily for 1–3 days or 1,000 mg in a single dose for adults or 10 mg/kg daily for 3 days for children, is recommended [20, 21]. Azithromycin is the empiric drug of choice for children and pregnant women. Rifaximin, 200 mg three times daily orally for 3 days, is an effective choice for people traveling to countries where noninvasive *E. coli* is common, such as Mexico [20]. Rifaximin does not effectively treat *Campylobacter* or *Shigella*, however [21]. Loperamide is considered safe to use in individuals older than 2 years of age when combined with antibiotic therapy and can usually help reduce symptoms to 1 day. As opposed to bismuth subsalicylate, loperamide is also safe for use in pregnant women. Oral rehydration therapy is also important, because dehydration is the main complication. Children can continue their usual feeding regimens including breast-feeding on demand. In those who do not respond to antibiotics, parasitic causes should be evaluated [20].

7 Hemorrhagic *E. coli* Colitis

7.1 Overview

In North America, *E. coli* O157:H7 is the most common Shiga-toxin-producing *E. coli* strain and the most common cause of hemolytic uremic syndrome (HUS) and hemorrhagic colitis [22, 23]. A popular misconception is that ground beef is a common vehicle of transmission and that outbreaks are common. Actually, most cases are sporadic, and ground beef transmission is not common, though it can occur due to internalization of the organism during processing [23, 24].

7.2 Clinical Presentation

Clinically, *E. coli* O157:H7 infection can range from asymptomatic to diarrhea (70–90% bloody) with complications of HUS or thrombotic thrombocytopenic purpura (TTP). After an incubation period of 1–7 days (3 days on average), abdominal cramps are initially followed by 1–3 days of watery, non-bloody diarrhea. Bloody diarrhea begins on the second to third day of illness. Fever is not a common finding, occurring in less than 30% of cases, and vomiting occurs in about 30–60% of cases [22, 24]. Abdominal pain is usually worse than in gastroenteritis caused by other bacterial pathogens, and patients may have abdominal tenderness on examination and painful defecation [23]. Overall mortality from these infections is 3–7% [24]. The complication of HUS appears 2–14 days after the onset of diarrhea and occurs in 2–15% of cases [22, 24]. Complications are more common in children and the elderly, with the most consistent risk factor for development of HUS being age less than 5 years or greater than 65 years. The mortality rate from HUS has been reported to be 3–17%, but has been seen as high as 87% in the elderly [24].

7.3 Etiology

The reservoir of infection is in the gut of cattle [24]. Modes of transmission include large herbivore (bovine) contact, contact with infected water that may have run off from grazing land, ingesting contaminated water, ingesting unpasteurized milk, ingesting unwashed salad or other vegetables (e.g., lettuce, radish, sprouts), day care centers, and person-to-person contact [23, 24]. Fecal shedding of *E. coli* O157:H7 may last for up to 2 months after acute infection, but a patient is most contagious during the acute diarrheal phase [22, 23]. The Shiga toxin is the main cause of the clinical features of this disease. The Shiga toxin mediates both the local and systemic disease [23, 24]. Local intestinal effects cause the development of bloody diarrhea with hemorrhage and edema of the lamina propria. HUS results from microvascular disease when the Shiga toxin enters the vasculature and binds to receptors on endothelial cells that are abundant in the kidneys, brain, and red

blood cells. A pro-inflammatory reaction occurs which triggers endothelial damage, TTP, hemolysis, and occlusion of renal and cerebral microvasculature. This reaction leads to renal failure and other complications, such as seizures and cerebrovascular accidents. Laboratory markers of HUS development include decreasing hemoglobin levels, fragmented RBCs on pathology, increasing LDH, decreasing platelet count, and increasing creatinine and blood urea nitrogen levels [24]. The treatment of HUS is beyond the scope of this text.

7.4 Treatment

Antibiotics are not recommended in the treatment of *E. coli* O157:H7, as drugs like TMP–SMX and fluoroquinolones can induce production of the Shiga toxin and thus increase the risk of developing HUS [16, 23, 24]. There is also no evidence to show decreased duration of illness or increased fecal excretion of the pathogen with antibiotic use [23]. Antimotility drugs, narcotic pain medicine, and NSAIDs are also not recommended [23]. Supportive care is the only recommended care at this time [16]. Intravenous rehydration has been recommended for its renal protective properties [23]. The best treatment for *E. coli* O157:H7 infection is prevention. This includes proper food and kitchen hygiene and reduction of contact with farm animals [24].

8 Non-hemorrhagic *E. coli*

8.1 Overview

Enterotoxigenic *E. coli* (ETEC) is the most common cause of bacterial gastroenteritis in the world, accounting for 20% of cases. It is the most common of the six types of diarrhea causing *E. coli* and is a frequent cause of diarrhea in children less than 2 years. About 25% of cases occur in adults.

8.2 Clinical Presentation

Overall, the clinical picture mimics that of *Vibrio cholerae*. Symptoms include vomiting and watery diarrhea with varying levels of dehydration. Fever is not common. The diarrhea usually persists for 3–4 days and is self-limited. Diagnosis is made by detection of the toxins in the stool.

8.3 Etiology

It is commonly found in countries such as Mexico, Bangladesh, Egypt, and Thailand. Infection is usually due to the ingestion of contaminated food and water and illness is caused by toxins formed by the pathogen.

8.4 Treatment

Treatment is supportive, with rehydration being the most important factor. With proper hydration, mortality is less than 1%. Adding zinc to the therapy has been found to reduce the duration of illness in children [25]. Please refer to Section 5 for antimicrobial options.

9 Campylobacter

9.1 Overview

Campylobacter species are the most common cause of bacterial gastroenteritis in the developed world [26, 27]. About 400 million cases occur worldwide, and only 2.5 million of these happen in the United States [27]. Risk factors for disease include males less than 5 years or 20–29 years, recent foreign travel, handling and ingestion of raw or undercooked poultry, unpasteurized dairy, contaminated water, ingestion of poultry at a restaurant, and contact with farm animals [26, 28].

9.2 Clinical Presentation

Symptoms occur 1–10 days after exposure and include diarrhea (possibly bloody), abdominal pain, fever, and occasionally vomiting. Some patients may be asymptomatic. Symptoms generally resolve in 2–5 days. Serious complications include reactive arthritis, which occurs in 1% of patients, and Guillain–Barre syndrome, which occurs in 0.1% of cases [26, 29]. Five to ten percent of patients need hospital admission, and mortality is 0.05%. Diagnosis is only through isolation of the pathogen in stool specimens because the symptoms are similar to many other bacterial gastrointestinal diseases [26].

9.3 Etiology

Campylobacter jejuni is the most common cause of disease, accounting for about 90% of cases, and is isolated from poultry, cattle, sheep, and goats [26, 27]. Disease occurs from the ingestion of contaminated poultry, red meat, water, or unpasteurized milk [27].

9.4 Treatment

Treatment is supportive, since most cases are short in duration and self-limiting. Antibiotics can be considered if the patient has severe or prolonged illness, and the drugs of choice are erythromycin and azithromycin [26, 27, 29]. Ciprofloxacin and

tetracycline are other alternatives, but ciprofloxacin resistance emerged after fluoroquinolones were added to feed for farm animals [26, 27]. Macrolide resistance has been reported in the range of 0.6–12% depending on the country. This antibiotic resistance is important because macrolide-resistant *Campylobacter* species have been associated with more severe illness [27, 29]. Prevention includes infection control at the farm level down to proper washing and cooking of meat and poultry and proper hand washing at the individual level [26].

10 Non-typhoidal *Salmonella*

10.1 Overview

In the United States, one of the most common bacterial causes of gastroenteritis is non-typhoidal *Salmonella enterica*. Salmonellosis accounts for about 30% of deaths, due to food-borne illnesses in the United States [30].

10.2 Clinical Presentation

There are a wide range of clinical presentations for non-typhoidal salmonella infections, but the most common presentations include acute onset of fever, watery diarrhea, and abdominal cramping [31, 32]. Illness usually occurs about 6–72 h after infection. Fecal shedding occurs for up to 1 month in adults and 7 weeks in children less than 5 years of age [31]. Approximately 5% of individuals with gastrointestinal illness caused by non-typhoidal *Salmonella* will develop bacteremia. This is important because a possible complication of this is the development of infectious endarteritis, especially of the abdominal aorta, which has been found to carry up to 38% mortality [31]. Focal infections can also occur, as there have been reports from Asia and Africa of meningitis, subdural empyema, and brain abscess as a complication of non-typhoidal *Salmonella* infection [32].

10.3 Etiology

More than 95% of cases of *Salmonella* infection are food-borne; outbreaks are generally caused by contaminated eggs, poultry, dairy, and beef [28, 30, 31]. Contaminated pork, fruit, and vegetables can also cause disease. It is also important to remember that reptiles (particularly lizards, snakes, and turtles) and amphibians (particularly frogs and newts) have *Salmonella* in their gastrointestinal tracts in up to 90% of individual animals [28, 30]. The amount of households in the United States with these animals as pets has significantly increased, and about 6% of non-typhoidal *Salmonella* infections each year can be attributed to contact with them [30]. The highest incidence of non-typhoidal *Salmonella* infections is in children less than 1 year of age. The risk factors for this population include riding in a shopping cart next to meat or poultry, exposure to reptiles, ingesting concentrated baby

formula up to 5 days before infection, day care, and travel outside the United States [28, 30]. Breast-feeding has found to be a protective factor in this population [28].

10.4 Treatment

For over the past 10 years due to their growth-promoting effects, antibiotics have been added to animal feed. However, this practice has bred resistance to these drugs such as fluoroquinolones in *Salmonella* species [28, 32]. Fluoroquinolones have been shown to possibly decrease the duration of symptoms by 1–3 days. However, there has been no benefit shown in reducing the time to stool clearance of the pathogen [31]. The mainstay of treatment is supportive care. Antibiotic treatment is not recommended for otherwise healthy individuals but is recommended for those who are severely ill [31, 33]. Children less than 1 year of age should be treated, especially those less than 3 months [31]. First-line drugs for *Salmonella* infection include fluoroquinolones, TMP–SMX, ampicillin, and third-generation cephalosporins, the latter being the preferred antibiotic for children. In the 1990s, increasing resistance to ampicillin and TMP–SMX was found. During this period of time the emergence and spread of *Salmonella typhimurium* definitive phage type 104 (DT104) began, which is resistant to these two drugs as well as streptomycin, tetracycline, and chloramphenicol [31, 33]. In the early 2000s, this subtype was found to account for 8–9% of *Salmonella* isolates in the United States [31]. Multidrug-resistant strains are more virulent than sensitive strains, having a reported 10-fold increase in mortality rate [32]. As with many of the infections mentioned in this chapter, prevention is the key to controlling these diseases. Many *Salmonella* infections can be prevented by hand washing; proper cleaning of cooking utensils and cooking surfaces; and thorough cooking of eggs, meat, and poultry [30].

11 Typhoid Fever

11.1 Overview

Typhoid fever is common throughout the world. The CDC estimates that there are 21.6 million typhoid cases each year, with about 200,000 patients dying annually. The majority of these cases occur outside the United States [34].

11.2 Clinical Presentation

Common clinical features of the disease include high-grade fevers, diarrhea, vomiting, abdominal pain, myalgias, and hepatomegaly. Other features could include toxicity, splenomegaly, headache, intestinal perforation, jaundice, and ileus. The gold standard for diagnosing typhoid fever is a positive blood culture, which occurs in only 40–60% of cases. Much of the diagnosis of typhoid fever is made clinically, which is difficult because it shares features with many other illnesses [34].

11.3 Etiology

Typhoid fever is caused by *Salmonella typhi*. A milder illness is caused by *S. paratyphi*. Disease caused by *S. typhi* is about 10 times more common than that caused by *S. paratyphi.* Mode of transmission is commonly through ingestion of contaminated water or food. Person-to-person transmission through poor hygiene and a contaminated water supply are also common [34].

11.4 Treatment

First-line treatment was previously with chloramphenicol or amoxicillin. In the 1990s, multidrug-resistant typhoid emerged and led to widespread use of fluoroquinolones for treatment. In recent years, fluoroquinolone resistance has been reported in Asia. The World Health Organization still recommends fluoroquinolones as the first-line treatment. In cases of quinolone resistance, ceftriaxone or azithromycin can be used. Two typhoid vaccines are available in the United States, with 60–80% efficacy, and should be taken at least 2 weeks before travel. One is an oral vaccine, which is contraindicated in pregnant women, children under 6 years, and immunocompromised patients. A booster may be required every 5 years. An intramuscular vaccine is available for travelers older than 2 years, and a booster may be required every 2 years [34]. Combined hepatitis A/typhoid fever vaccines are not licensed in the United States, but are available in Europe, and have been shown to be safe and effective [35].

12 *Shigella*

12.1 Overview

There are 140 million cases and over 600,000 deaths each year from *Shigella* species infection, known as shigellosis or acute bacillary dysentery. It is a disease commonly seen in children in developing countries and can be attributed to overcrowding and unsanitary living conditions [36].

12.2 Clinical Presentation

The symptoms of shigellosis are passage of loose stools mixed with blood and mucus, fever, crampy abdominal pain, and tenesmus. Cases range from asymptomatic and mild (typically produced by *Shigella sonnei*) to severe (typically produced by *S. flexneri* or *S. dysenteriae* type I). Some children can experience fevers up to 104°F, convulsions, rectal prolapse, and even malnutrition. *S. dysenteriae* type I infection may cause arthralgias, hemolytic uremic syndrome, intestinal

perforation, hemorrhage, and toxic megacolon. Diagnosis is made by the clinical presence of blood and mucus in the stool along with many fecal leukocytes seen on microscopic stool exam and confirmation by stool culture [36].

12.3 Etiology

The mode of transmission is fecal–oral, and it takes as few as 10–100 organisms to cause infection. It is commonly transmitted by person-to-person contact or by contaminated water and food, such as raw vegetables. An infected individual is contagious as long as they excrete the organism in the stool, which can last for up to 4 weeks [36].

12.4 Treatment

Antibiotic treatment in shigellosis has been shown to reduce the duration of diarrhea by an average of 2.4 days [16]. Effective therapies in the past have included trimethoprim–sulfamethoxazole, tetracycline, ampicillin, and nalidixic acid, but increased bacterial resistance now limits their efficacy [16, 36]. Drugs that are commonly used now include the fluoroquinolones (particularly ciprofloxacin, 500 mg orally twice daily for 3–5 days), but even these have shown increasing resistance in countries such as India and Bangladesh over recent years [36]. Ciprofloxacin is the only fluoroquinolone that has been shown to be safe in children [16]. The only antibiotics shown to be effective in multidrug-resistant shigellosis are ceftriaxone and azithromycin. Treatment should also include oral rehydration and small, frequent meals. The most important prevention strategy is frequent hand washing with plenty of soap and water [36]. There is no commercial vaccine available at this time for shigellosis [17, 36].

13 *Vibrio cholerae*

13.1 Overview

Cholera is caused by *V. cholerae* and is generally indistinguishable from other types of acute bacterial diarrhea. Cholera only affects the intestine and does not produce systemic symptoms. Cholera is endemic in Africa, Asia, Central America, and South America [37].

13.2 Clinical Presentation

Symptoms of vomiting and voluminous “rice-water” diarrhea develop abruptly. Adults with severe cholera may lose ½ to 1 l of fluid per hour, leading to severe

dehydration [38]. About 90% of cases are mild to moderate in severity [37]. In severe cases, cholera can cause 50% mortality if left untreated, mostly within the first day of illness. This can be reduced to 1% with adequate supportive care [37, 38].

13.3 Etiology

The disease is caused by a toxin produced from the bacteria that binds to the intestinal mucosal cells and causes diarrhea and dehydration [37]. The incubation period is 18–120 h [38]. The mode of transmission is fecal–oral, and epidemics can occur after disasters where water and food supplies become contaminated [37]. A dose of 100,000 to 100 million bacteria is required for infection in healthy individuals because gastric acid is protective against infection, acting as a natural barrier [37, 38]. In those who have decreased gastric acid levels, such as patients with *H. pylori*, a lower infectious dose can cause infection [37]. Other risk factors include poverty, lack of development, high population density, low education, and lack of previous exposure [39].

13.4 Treatment

The mainstay of treatment of cholera is replacement of fluids, orally for mild disease with no signs of dehydration, intravenously for severe disease. Doxycycline 300 mg daily for 1–3 days is the preferred antibiotic. Patients will recover in about 4–5 days with supportive treatment alone, and about 2–3 days with antibiotic treatment. Patients with mild disease should not receive antibiotics and prophylaxis is not recommended [38].

In the last 20 years, there have been reports of resistance to tetracycline, ampicillin, kanamycin, streptomycin, sulfa drugs, trimethoprim, and gentamicin. Fluoroquinolones have been effective, but quinolone resistance has been reported in India [38]. Prevention of cholera is achieved by having satisfactory sanitation and clean drinking water [37]. Oral cholera vaccines have been shown to be effective without serious side effects [38].

14 *Yersinia*

Infection with *Yersinia enterocolitica* is not common, with the CDC estimating only about 17,000 cases each year in the United States [40]. A well-known mode of transmission is through the ingestion of raw or undercooked pork [40, 41]. *Yersinia* is unique in its ability to survive and reproduce at temperatures close to 0°C [42]. Infection usually affects young children, where symptoms are non-specific and include fever, diarrhea (sometimes bloody), and abdominal pain. In adults, symptoms include abdominal pain that mimics appendicitis. Symptoms develop 1 week after exposure and last for 3–28 days in children and 1–2 weeks in adults.

Complications include monoarticular arthritis, erythematic nodosum, and reactive polyarthritis, the latter in patients who are HLA-B27 positive [40, 43]. Diagnosis is determined by stool or blood culture. Most cases are self-limited. Antibiotic treatment does decrease seriousness and length of illness. *Y. enterocolitica* in vitro is susceptible to aminoglycosides, tetracyclines, TMP–SMX, and ciprofloxacin. It is resistant to penicillin, ampicillin, and first-generation cephalosporins. Prevention includes hand washing and avoiding raw meat, unpasteurized milk, and unchlorinated water [40].

15 *Bacillus*

Bacillus cereus causes two types of illness: diarrhea and emesis. The diarrheal type, which is caused by heat-labile toxins, is found in meats, soups, vegetables, sauces, and dairy. The emetic type, which is caused by a heat-stable toxin, is found in rice, noodles, pasta, and pastry. Illness occurs because the spores of the pathogen are hardy and can survive cooking or pasteurization. They then germinate and multiply in food that is not properly refrigerated. The incidence of the disease is not fully known, due to frequent misdiagnosis and since the symptoms are commonly confused with other gastrointestinal illnesses. Diarrheal illness starts 8–16 h after ingestion whereas the emetic illness starts 30 min–6 h after ingestion. Both types of disease are mild and usually resolve within 24 h [44].

16 *Listeria*

Infection with *Listeria monocytogenes* is rare, with an incidence of only about 0.7 case per 100,000 individuals [45]. Most reported cases are of bacteremia and meningitis caused by the pathogen and are beyond the scope of this chapter [46]. Infection can also present as a febrile gastroenteritis, which is rare and self-limiting. This infection is characterized by fever and non-bloody diarrhea within 24–48 h of ingestion of contaminated food and resolves spontaneously. Outbreaks have occurred with Mexican-style cheeses, as well as chocolate milk, various deli meats, rice salad, corn salad, and shrimp [45, 46]. *Listeria* can survive in near-freezing temperatures, similar to bacillus species [46]. To avoid infection, individuals should avoid raw milk and soft cheeses, especially in pregnant women and the elderly [45].

17 *Clostridium difficile*

17.1 Overview

Clostridium difficile is the most common cause of infectious diarrhea in hospitalized patients and one of the top four most common infections in nursing home residents. It is the organism responsible for 3 million cases of diarrhea each year and

about one-fifth of cases of antibiotic-associated diarrhea [47, 48]. Mortality from *C. difficile*-associated diarrhea (CDAD) is 17% overall, with a higher percentage in the elderly.

17.2 Clinical Presentation

Common clinical signs of CDAD include mild to moderate watery diarrhea, lower abdominal pain and cramping, fever, malaise, nausea, anorexia, and leukocytosis [47–49]. In the elderly, they may present with altered mental status, weakness, and weight loss [48]. Colitis can develop in 1–3% of patients. Clinical signs include diffuse abdominal pain, distention, and high fever. Those who are the most severely ill may develop toxic megacolon, which has an overall mortality of 25–40% or possibly bowel perforation [47, 49]. Recurrent diarrhea occurs in 10–40% of patients treated [49]. The gold standard for diagnosis is testing for *C. difficile* toxins in a stool sample, particularly toxin B, which has a specificity of 99–100% if found [48].

17.3 Etiology

The mode of transmission is by the fecal–oral route. A patient is colonized by exposure to *C. difficile* spores, and if there is a disturbance of the normal colonic flora, usually by recent antibiotic use, then the patient is at increased risk to develop the disease [48].

The most frequent antibiotics associated with this are clindamycin and the cephalosporins [49]. *C. difficile* binds to colonic mucosa and produces two toxins, known as cytotoxin A and B. These toxins work in tandem, with toxin B thought to be 1,000 times more powerful than toxin A. They work to break down the tight junctions between mucosal cells, thus causing cellular leakage and thus watery diarrhea. If the infection is left untreated, then apoptosis of cells occurs, causing ulceration of the gut mucosa and subsequent development of pseudomembranes, leading to pseudomembranous colitis [48].

There have been increasing reports of a hypervirulent strain of *C. difficile* from North America and Europe over the past 8 years [49, 50]. This strain is known as the pulse field type 1, PCR ribotype 027 (NAP1/027) strain. This strain produces 16 times the amount of toxin A and 23 times the amount the toxin B than wild-type *C. difficile* [49]. Type 027 strains have been found to have high-level fluoroquinolone resistance and thus exposure to these antibiotics is a major risk factor for developing CDAD caused by these strains [49]. High relapse and mortality rates have been reported with this strain, especially in the elderly [51]. Type 027 strains isolated from Canada were found to be susceptible to clindamycin, metronidazole, vancomycin, meropenem, and rifampin. However, they were resistant to bacitracin, clarithromycin, cephalosporins, and fluoroquinolones [49].

17.4 Treatment

The first step in treatment of this infection is to discontinue the antibiotic contributing to the infection [47, 48]. In patients with mild to moderate infection, first-line treatment is oral metronidazole, 250–500 mg every 8 h or oral vancomycin, 125 mg every 6 h, for 10–14 days. Clinical improvement occurs in 85–95% of patients within 5 days [47, 48]. Vancomycin is safe in women who are pregnant or breast-feeding. Both antibiotics have showed response rates of 85% in the past, but in recent years metronidazole response rates have dropped to 62–74% [47]. Part of this can be attributed to the hypervirulent *C. difficile* strain (see above) that has emerged over the past few years.

Relapse occurs in about 25% of cases, and these cases are usually treated with a repeat course of vancomycin or metronidazole. For severe and refractory cases, intracolonic vancomycin, enemas of "donor stool," surgery (total colectomy), and intravenous immunoglobulin (IVIG) are all options [47, 50]. However, the effectiveness of IVIG has not been established in randomized control trials [51].

Prevention of the spread of *C. difficile* is crucial. The simplest methods include frequent hand washing with soap and water, cleaning contaminated surfaces with bleach, and contact isolation precautions with infected patients [48]. Probiotics, such as *Lactobacillus*, have shown modest benefits in some trials, but no probiotic has reliably been effective as prophylaxis and thus remains controversial [49–51]. Vaccines that contain inactivated toxins A and B have been developed, but trials to test them have yet to occur [49, 50].

18 Parasites

18.1 Giardia

18.1.1 Overview

Giardia intestinalis aka *Giardia lamblia* is the most common gastrointestinal protozoal infection in humans [52]. It is estimated that over 280 million people are infected annually, but that most of these patients are in developing nations with a prevalence of only about 2–7% in developed countries.

18.1.2 Clinical Presentation

Many patients with *Giardia* infection are asymptomatic, but those that are affected can have a range of symptoms, which include nausea and vomiting, abdominal cramping, and diarrhea. The most severe cases can occur in children with a failure-to-thrive syndrome that results from chronic diarrhea and malabsorption. Symptoms usually occur about 7–14 days after infection and can persist from a few days to several weeks [52, 53]. No gold standard exists for diagnosis, but the first method usually chosen is stool examination to attempt to observe the cysts or trophozoites

of the pathogen. If direct stool examination is negative, then other diagnostic options include examination of duodenal aspirate and stool ELISA [52].

18.1.3 Etiology

Modes of transmission include contaminated water and food and person-to-person transmission by a fecal–oral route during sexual activity [53]. Patients found to be at the highest risk include travelers to foreign countries (especially Mexico, South America, Asia, Africa, and the former Soviet Union), children in day care, and homosexual men [52].

18.1.4 Treatment

The first-line treatment regimen is metronidazole, 250 mg three times daily for 5–10 days [52, 53]. If this is not effective, a higher dose regimen of 500–800 mg, three times daily for 5 days, can be used [52]. Resistance to metronidazole is reported in 20% of cases, with recurrence of *Giardia* infection in up to 90% of cases. An effective alternative to metronidazole is tinidazole, 100 mg three times daily for 7 days. The recommended regimen for pregnant patients is paromomycin, 500 mg three times daily for 5–10 days. If cases are refractory to treatment with metronidazole or tinidazole, then other possible drugs that could be used are furazolidone, quinacrine, and albendazole [53].

19 *Entamoeba histolytica*

Entamoeba histolytica is estimated to have infected over 50 million individuals worldwide, causing 40,000–110,000 deaths each year. Most cases occur in developing countries. Many patients are symptomatic, but those that do develop symptoms generally have bloody diarrhea with abdominal pain. Fever is rare. Infection occurs from ingestion of cysts in contaminated water. The cysts develop into the active amoeba, which destroys epithelial cells in the bowel. The drug of choice for treatment is metronidazole 750 mg three times daily for 7 days. Cyst carriers should be treated for at least 10 days. To date, there are no reports of high levels of metronidazole resistance [53].

20 Cryptosporidium

20.1 Overview

Infection with *Cryptosporidium* species affects about 300,000 patients in the United States annually. In developing countries, it is found in an average of 12.7% of cases

of diarrhea. Peak incidence is in warm months, with a peak in the United States from July through September [54].

20.2 Clinical Presentation

Cryptosporidium is associated with HIV infection and is found in approximately 16% of patients who have AIDS and diarrhea. Symptoms occur about 1 week after infection and commonly present as watery diarrhea with malabsorption. AIDS patients with a CD4 count less than 50 can present with more severe disease which is similar to cholera with voluminous watery stools. Diagnosis is by microscopic examination of stool [54].

20.3 Etiology

Infection with this pathogen is associated with ingestion of contaminated drinking water. Other infections have been documented with contaminated recreational water, such as swimming pools. Food-borne infections are less common, but associated with apple cider, unpasteurized milk, chicken salad, and raw produce. Person-to-person transmission is common, because cysts shed in the stool are virulent, and has been associated with outbreaks in day care centers and hospitals [54].

20.4 Treatment

Treatment includes fluid and electrolyte replacement, with oral rehydration being the preferred method. Antimotility drugs have been shown to decrease symptoms in mild cases. In AIDS patients, antiretroviral therapy has shown to improve diarrhea. Antibiotics to consider include nitazoxanide, 500 mg twice daily for 3 days, and paromomycin, 500 mg three times daily for 5–10 days [54].

21 Diverticulitis

21.1 Overview

Diverticular disease of the colon is rare in developing nations, but a common problem in the Western hemisphere. Diverticular disease includes diverticulosis and diverticulitis. Diverticula are outpouchings that occur at weak points of the colonic wall where small blood vessels enter the circular muscle layer [55]. Diverticulosis is associated with a diet high in fat, high in refined carbohydrates, and low in fiber [55, 56]. Other risk factors include physical inactivity, constipation, obesity, smoking,

and non-steroidal anti-inflammatory (NSAID) use [56]. The incidence of diverticulosis increases with age. Approximately one-third of the population greater than 45 years and 50–70% of the population greater than 80 years have diverticulosis. Sixty-five percent of patients have disease at the level of the sigmoid colon.

21.2 Clinical Presentation

Fever, malaise, and left lower quadrant or suprapubic abdominal pain are common presenting symptoms. Patients may also present with change in bowel habits, nausea, vomiting, and urinary symptoms [55]. Abdominal or perirectal fullness may also be present [56]. A tender mass in the left lower quadrant is the most common finding on physical exam [55]. A complete blood count usually demonstrates an elevated white blood cell count with a left shift. A computed tomography (CT) scan is the best radiologic study to aid in the diagnosis of diverticulitis. It has a sensitivity of 85–97% and a specificity of almost 100% [55, 56]. The presence of diverticula, inflammation of the pericolic fat or other tissues, bowel-wall thickness greater than 4 mm, or a peridiverticular abscess suggests the diagnosis of diverticulitis [56]. Colonoscopy is contraindicated in patients who have acute diverticulitis because of the increased risk for perforation, but can be performed 6 weeks after resolution of the acute disease process [55, 56].

21.3 Etiology

The pathogenesis of diverticulitis is not fully known. It is thought that it is a complication of diverticulosis that occurs when these outpouchings become infected and possibly perforated [55, 56]. Diverticulitis occurs in 15–20% of patients who have diverticulosis [55]. Anaerobes are the most commonly isolated organisms, along with *E. coli* and streptococci [56].

21.4 Treatment

Patients who have mild diverticulitis (i.e., those patients who can tolerate oral intake and who have only mild symptoms with no peritoneal signs) can be treated as an outpatient with 7–10 days of broad-spectrum oral antibiotics that include coverage against anaerobic bacteria [55, 56]. Treatment regimens can be found in Table 2. A clear liquid diet is recommended until symptoms resolve. Then the diet can be advanced slowly as tolerated by the patient. Symptoms should improve within the first 2–3 days.

Hospitalization is indicated if the patient is unable to tolerate oral intake or has increasing pain or fever. In this case, the patient should not be allowed anything by mouth (NPO) and intravenous fluids and antibiotics should be started [55, 56].

Table 2 Treatment regimens for diverticulitis

Oral
1. Metronidazole, 500 mg every 6–8 h *and* ciprofloxacin, 500–750 mg every 12 h
2. Metronidazole, 500 mg every 6–8 h *and* trimethoprim–sulfamethoxazole (TMP/SMX), one double strength tablet every 12 h
3. Amoxicillin–clavulanic acid, 875 mg every 12 h
Intravenous
1. Metronidazole, 500 mg every 6–8 h *and* ciprofloxacin, 400 mg every 12 h
2. Metronidazole, 500 mg every 6–8 h *and* ceftriaxone, 1–2 g every 24 h
3. Ampicillin–sulbactam, 3 g every 6 h

Information from [56]

Intravenous regimens can also be found in Table 2. Improvement should occur in 2–3 days. If it does not, surgical intervention or percutaneous drainage of a possible abscess may be necessary. Computerized tomographic (CT) imaging may be helpful in these steps. If the patient does respond to IV antibiotics, then the patient can be switched to one of the oral regimens to complete a 7–10 day course, and diet can be slowly advanced as the patient tolerates. Fifty to eighty-five percent of patients respond well to antibiotics during their first episode of diverticulitis, and only less than 10% require surgical intervention [55, 56].

22 Human Papilloma Virus and Anal Cancer

Squamous cell carcinoma of the anus is a rare tumor that accounts for 1.5% of all cases of gastrointestinal tract cancer in the United States. Its incidence has risen over the last 25 years to a current incidence of 1.5 per 100,000. It occurs more frequently in men who engage in anoreceptive intercourse and in these patients with HIV infection [57, 58]. Other risk factors for anal cancer include low CD4 count, cigarette smoking, immunosuppressant therapy following transplants, history of persistent high-risk human papillomavirus (HPV) infection, and infection with multiple HPV genotypes [57]. HPV has been detected in up to 90% of anal cancers with HPV subtype 16 being the most common, appearing in about 70% of cases [57–59].

In the past few years, one of the major developments that promises to have an impact on reducing the incidence of anal cancer is the prophylactic HPV vaccine [58, 59]. The vaccine currently available in the United States and many countries in Europe protects against HPV subtypes 6, 11, 16, and 18. In phase III trials, it was shown to have 100% efficacy at preventing disease from these subtypes. The vaccine is administered in three total doses: one initial dose, then another dose each at 2 and 6 months after the initial dose. It has been shown that this vaccine is purely for prophylaxis, as it will not be effective in those who already have HPV

infection. Currently, the vaccine has only been approved for females aged 9–26 years. It has not been approved for use in males; however, studies are promising. In one study, antibody levels were found to be higher in 9- to 15-year-old boys than in girls of the same age group [59]. Therefore, there is potential that this vaccine could reduce the incidence of anal cancer in not only females but males as well.

23 Inflammatory Bowel Disease

23.1 Overview

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract. IBD has been shown to occur in genetically susceptible patients, particularly those with a defect in the NOD2/CARD15 gene. A defect in this gene causes an aberrant immune response to enteric flora and dietary factors [60, 61]. Most IBD lesions occur in the distal parts of the GI tract, where bacteria are the most numerous [60].

23.2 Etiology

There is evidence that the enteric flora themselves play an important role in the development of IBD. Patients with IBD have higher concentrations of enteric bacteria and an altered balance of these bacteria, which is known as dysbiosis [60, 61]. This altered composition has been found to contain increased concentrations of aggressive bacteria, such as *Bacteroides* species and *E. coli*, and decreased concentrations of protective bacteria, such as *Bifidobacterium* and *Lactobacillus* species. Some studies have shown that dysbiosis may be the trigger for the chronic inflammation associated with IBD [61, 62]. Recent research in mice suggests that a possible deficiency in a transcription factor that regulates tumor necrosis factor production in mucosal cells may contribute to increased inflammation when these cells have an exaggerated response to gastrointestinal flora [63].

23.3 Treatment

Antibiotics have widely been used for the septic complications of IBD, which include abscesses, peritonitis, fistulae, fissures, and toxic megacolon. However, the use of antibiotics as primary treatment or as adjunctive treatment (with aminosalicylates and steroids) has not been established. Despite this lack of evidence, they are still frequently used. Metronidazole and ciprofloxacin are the most widely studied antibiotics with mixed results [61]. Rifaximin has shown promise in early studies, with safety and efficacy in CD, UC, and pouchitis, showing both positive

clinical and endoscopic results [60, 61]. There is a concern for development of *C. difficile*-associated diarrhea with frequent antibiotic use as well as future antibiotic resistance.

Overall, antibiotics have not been found to be superior to other treatments nor do they increase efficacy of these other treatments in CD. Metronidazole and ciprofloxacin in particular have been found to be as effective as aminosalicylates and steroids [61, 64]. However, they have been shown to be more effective than placebo [60, 64]. There has also been evidence found of increased efficacy in colonic disease versus ileal disease. If the patient does have acute left colonic disease, metronidazole (10–20 mg/kg/day), ciprofloxacin (500 mg twice daily), a combination of these two antibiotics, or rifaximin (400 mg twice daily) can be treatment options [61].

Antibiotics studied in UC have shown no benefit except in the case of pouchitis [60, 61]. Twenty-five to thirty-two percent of patients with UC will require surgical treatment. The preferred procedure in this case is a total colectomy with ileal pouch–anal anastomosis, and the most common complication of this surgery is an inflammation of the pouch reservoir, known as pouchitis. Within 5 years of the surgery, the risk of developing an acute episode of pouchitis is 50% and there is a 5% chance of developing chronic pouchitis. For treatment of pouchitis, a regimen similar to that for acute left colonic CD is recommended. Clinical improvement is generally seen in 1–2 days. However, in chronic pouchitis, antibiotics have been shown to have a lower efficacy [61].

As mentioned above, there is evidence showing that there is immunological intolerance to enteric bacteria in patients with IBD, leading to the proposal that manipulation of the enteric flora with probiotics may be therapeutic in IBD. Most evidence supports the use of probiotics in pouchitis [61, 62]. Most trials have used a probiotic mixture known as VSL#3, which contains a very high bacterial concentration (each packet containing 450 billion viable bacteria) of eight different bacterial specie: four strains of lactobacilli, three strains of bifidobacteria, and one strain of *Streptococcus salivarius* subsp. *thermophilus* [62]. Several studies have found that giving VSL#3 after antibiotics for pouchitis has beneficial results. There is also some promising results using VSL#3 in UC and CD [61, 62]. Overall, more study is needed on this subject.

24 Hepatitis

24.1 Hepatitis A

24.1.1 Overview

Hepatitis A infections have significantly decreased since the introduction of two effective vaccines in the United States in the mid-1990s. From 1990 to 2004, the number of yearly cases dropped from 32,000 to 5,609 [65, 66]. In many industrialized countries, such as the United States, the immunization rate is lower than in developing nations due to improved hygiene and sanitation [67]. The

Hepatitis A virus (HAV) exists in freshwater, seawater, wastewater, and soil. It is able to resist detergents, acids, and freezing, but does not resist chlorine or formalin. Initial diagnostic tests for infection include liver function tests and hepatitis serology. Antihepatitis A IgM testing can be used as a confirmatory test, but should not be used as a screening test due to a high false-positive rate [65].

24.1.2 Clinical Presentation

In children, only 30% of those infected with HAV develop symptoms, which are usually flu like. Jaundice does not generally occur in infected children younger than 6 years. Children can shed the virus in their stool for up to 6 months, even those who are asymptomatic.

The vast majority of infected adults (greater than 80%) are affected for up to 8 weeks. In adults, about 70% of those infected develop symptoms, including jaundice. There are two phases to the illness: the pre-icteric and icteric phases. The pre-icteric phase is characterized by fever, malaise, anorexia, nausea, vomiting, abdominal pain, headache, tender hepatomegaly, splenomegaly, bradycardia, and posterior cervical lymphadenopathy that lasts for 5–7 days. The icteric phase is categorized by conjugated bilirubinuria followed by depigmented stools and jaundice that lasts for 4–30 days [65].

24.1.3 Etiology

The mode of transmission is the oral–fecal route. Often, this occurs by intake of contaminated food or water or person-to-person contact. In the United States, most food-borne infections of HAV are associated with ingestion of green onions and strawberries; outside the United States, shellfish is a major cause [65].

24.1.4 Treatment

Treatment is strictly supportive as there is no antiviral therapy available. This includes rest, balanced nutrition, and avoidance of alcohol, acetaminophen, and other hepatotoxins. Approximately 30% of symptomatic patients require hospitalization [65]. Prevention can be achieved with the hepatitis A vaccine, which can provide protection for 12 years in immunocompetent adults and for 6 years in children [67]. Lifelong immunity can only be achieved through infection [66]. Hepatitis A serum immune globulin can give short-term immunity for 3–5 months and can prevent infection in 80–85% of patients prior to exposure and in 69–89% of patients within 2 weeks of exposure to HAV [65].

24.2 Hepatitis B

24.2.1 Overview

Hepatitis B virus (HBV) commonly causes liver disease, with well over 1 million deaths each year. The incidence of the disease, however, has decreased in the United States over the past 20 years. From the late 1980s to 2001, the number of acute cases of HBV infection decreased from 300,000 to 79,000 per year. This is likely due to the development of the HBV vaccine, which will be discussed later in more detail [68].

24.2.2 Clinical Presentation

Acute HBV infection is characterized by nausea, anorexia, fatigue, low-grade fever, and epigastric or right upper quadrant pain. In 70% of adults and 90% of children less than 5 years of age, acute infection is subclinical. In 1–3 months, the symptoms of acute disease generally resolve. Alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin levels can all be elevated. In approximately 1% of acute infections, hepatic failure can occur from large-scale hepatocellular necrosis [68]. The following are the markers used in HBV infection: hepatitis B surface antigen (HBsAg), which is used to diagnose acute infection and carriers, hepatitis B core antibody (anti-HBc), which shows HBV infection at some point during the patient's life, hepatitis B core antibody IgM (IgM anti-HBc), which shows recent infection, hepatitis B e-antigen (HBeAg), which shows the patient is infectious when elevated, and hepatitis B surface antibody (anti-HBs), which shows recovery and/or immunity (natural or vaccine acquired) [66].

The criteria for chronic HBV infection are being HBsAg positive for more than 6 months, serum HBV DNA greater than 100,000 copies/mL, persistent elevation of ALT and AST, and a liver biopsy showing chronic hepatitis. Each year, 12% of patients with chronic HBV infection progress to cirrhosis, and a minority of these patients progress to hepatocellular carcinoma. In patients with chronic hepatitis B infection, their lifetime risk of death from cirrhosis or hepatocellular carcinoma is between 12 and 25%. Hepatocellular carcinoma can develop 25–30 years after developing chronic infection, and screening patients is controversial.

24.2.3 Etiology

HBV's mode of transmission is through blood and other body fluids such as saliva and semen. In the United States, Canada, and Western Europe about 80% of infections are transmitted sexually or by intravenous drug use. However, in China, Southeast Asia, and sub-Saharan Africa, 5–20% of infections are acquired during childhood or by vertical transmission from mother to child [68].

24.2.4 Treatment

The treatment for acute HBV infection is supportive care. For chronic HBV infection, the goal of treatment is to prevent end-stage liver disease by suppressing viral replication [68]. The first-line treatment is interferon-alpha, which causes seroconversion in 46% of patients within the first 12 months. However, it has many side effects and is not well tolerated. Lamivudine, a nucleoside reverse transcriptase inhibitor, is another medicine that can be used as first-line therapy or in patients who failed interferon. The main concern with this treatment is viral resistance, which develops at 15–20% per year of treatment; after stopping treatment, relapse is relatively common. A third treatment is adefovir dipivoxil, another reverse transcriptase inhibitor, which can be used after failure of lamivudine treatment. It has been shown to breed no resistance, but there is the risk of nephrotoxicity [66, 68].

The HBV vaccine has become a standard in medical care. It has been used for over 20 years and has been found to be safe and effective [67]. The vaccine is recommended for all children and also for high-risk groups, such as medical workers, intravenous drug users, patients with a history of sexually transmitted diseases or multiple sex partners, men who have sex with men, and hemodialysis patients. The vaccine is a series of three injections given over 6 months, with 95% effectiveness in children and 90% in adults. Due to its high effectiveness, the CDC recommends starting a vaccination series on all patients even if it might not be completed. The vaccine can be given safely during pregnancy. If a woman tests positive for HBsAg during pregnancy, then it is recommended for the infant to receive the HBV vaccine and HBV immune globulin within 12 h of birth, which reduces the risk of vertical transmission from 10 to 3% [68].

24.3 Hepatitis C

24.3.1 Overview

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States, with a prevalence of almost 3 million people [69]. HCV accounts for approximately 40% of chronic liver disease in the United States. HCV is the number one cause for liver transplantation in the United States [66, 69].

24.3.2 Clinical Presentation

Most patients with HCV show no symptoms. Only 20–30% of patients have jaundice during the acute phase. A hallmark of the disease is a fluctuating pattern of elevated alanine transaminase (ALT) [66]. Fifty to seventy percent of patients with acute HCV infection develop chronic hepatitis [72]. Seventeen percent of patients with chronic infection will develop cirrhosis, and chronic infection carries a mortality rate of 4% [66]. Patients with cirrhosis have a 1–2% annual risk of developing hepatocellular carcinoma [69].

There are two different diagnostic tests for establishing the presence of a hepatitis C infection. The first is an enzyme immunoassay screen that detects anti-HCV antibodies with a sensitivity of 98%. If this first test is positive, then a second test, a serologic anti-HCV assay or a nucleic acid test (e.g., polymerase chain reaction), is performed to confirm the diagnosis [66]. Liver biopsy is recommended to determine the need for antiviral therapy based on the degree of inflammation and amount of fibrosis [69].

24.3.3 Etiology

HCV's mode of transmission is infected blood and blood products. Intravenous drug use accounts for 60% of acute infections [66]. Other risk factors include household contact, dialysis for multiple years, accidental needle sticks, blood transfusions prior to 1992, intranasal cocaine use, sex with multiple partners, and body piercing [66, 69]. Household contacts and sexual partners of HCV-positive patients should be tested as they have been shown to have a higher prevalence than the general population [70]. The groups most at risk are people aged 25–40 years, African-Americans, and Mexican-Americans [66]. Co-infection with HIV is common; approximately 40% of Americans infected with HIV and up to 90% of intravenous drug users who have HIV are also infected with HCV. This is likely due to the two viruses' similar modes of transmission [69]. Chronic HCV infection has also been shown to increase the risk of other viral infections. Therefore patients with this disease should be immunized against HAV and HBV, as well as possibly varicella and influenza [71].

24.3.4 Treatment

Standard HCV therapy includes a combination of interferon-alpha (IFN) and ribavirin [66, 73]. Treatment lasts for 24–48 weeks depending on the genotype of hepatitis C present in the patient. Patients are considered cured when they have a sustained virologic response (SVR), defined as undetectable HCV RNA 6 months after therapy is completed [74]. The sustained response rates if IFN alone are only 10–20% [73]. Patients who are likely to have an SVR are females under 40 years without cirrhosis who do not ingest alcohol and have infection with genotypes 2 or 3 [66]. Multiple studies have also shown lower treatment response in African-American patients compared to Caucasian patients [72]. Patients over 60 years, uncontrolled substance abusers, and patients with a comorbid condition that is worsened by anemia are those in whom treatment with interferon is contraindicated [66]. HCV treatment is also contraindicated in pregnancy [66, 69, 74]. Ribavirin has no effect against HCV on its own and therefore is used only as adjunctive therapy with IFN. Pegylated IFN, a polyethylene glycol molecule attached to the IFN, has been shown to have SVR's of 54–60% when used in combination with ribavirin [73, 74]. This combination of drugs has become the standard of care for treatment of HCV infection [74]. The contraindications to ribavirin are severe anemia, ischemic heart disease, and renal failure because the drug is known to cause anemia [73]. Insomnia,

depression, and neutropenia are other well-known side effects of HCV treatment [69, 74].

24.4 Hepatitis D

Hepatitis D virus (HDV) is a virus that can only be replicated by the hepatitis B virus. The vast majority of patients with HDV infection (90%) are asymptomatic [66]. The mode of transmission is through blood and blood products, and a patient can only be infected with the virus if they already have HBV infection or are infected with both HBV and HDV simultaneously, which is seen mostly among IV drug abusers in the United States. Patients with preexisting HBV who develop an HDV superinfection have an 80% chance of developing chronic liver disease. There is no vaccine for HDV prevention. The current standard of care for treatment of HDV is interferon, which has limited efficacy. Recent studies support the use of pegylated interferon for treatment of HDV, but this is still experimental. Ribavirin has been shown to provide no additional benefit in these studies [72].

24.5 Hepatitis E

The hepatitis E virus (HEV) is similar to HAV in terms of size and structure. Clinical symptoms are similar to those of HAV infection, which include jaundice, fatigue, abdominal pain, anorexia, nausea, and vomiting [75]. HEV infection has also been shown to cause acute pancreatitis, particularly in young, male patients [76]. The gold standard to diagnose the infection is through polymerase chain reaction studies. Mortality of HEV infection is 1–4% in non-pregnant patients, but can increase to upward of 20% in pregnant females. HEV infection in utero can cause loss of the pregnancy [75]. The mode of transmission is through fecally contaminated water; transmission through contaminated food is rare. Infection is rare in the United States, but the virus has infected more than 2 billion people worldwide and is a cause of 20–40% of acute liver failure in endemic areas [75, 76]. HEV is usually associated with travel to areas such as North Africa and Southern Asia [66]. Treatment is supportive. Most important is prevention, which includes diligent hand washing and hygiene, avoiding consumption of water in known endemic areas, and ensuring that meats, especially pork, are well cooked. There is no vaccine for prevention that is commercially available at this time [66, 75].

25 Spontaneous Bacterial Peritonitis

25.1 Overview

One of the major complications of cirrhosis is spontaneous bacterial peritonitis (SBP). SBP carries a lifetime incidence of 10–30% and is the most common

infection in patients with cirrhosis [77]. SBP is defined as an infection of ascitic fluid with an ascitic fluid polymorphonuclear leukocyte (PMNL) count of greater than or equal to 250 cells/mm^3 in the absence of a known source of infection [77, 78]. Therefore, paracentesis should be performed in all patients who present with ascites to rule out SBP. Despite the fact that approximately 60% of cultures of ascitic fluid in SBP are negative, these should still be obtained. Cirrhotic patients with SBP have a reported mortality rate of 50–70% after 1 year and 70–75% after 2 years. This is due to the advanced stage of cirrhosis that is usually present in patients who develop SBP. The majority of the mortality is due to septic shock, multiorgan failure, and variceal bleeds. Therefore, patients who survive an episode of SBP should be evaluated for liver transplantation [77, 79].

25.2 Clinical Presentation

The majority of patients with SBP are asymptomatic, but some will present with fever, nausea, diffuse abdominal pain, renal insufficiency, or ileus [77, 79]. About one half of patients with SBP will develop encephalopathy [77].

25.3 Etiology

SBP is mainly caused by gram-negative bacteria, particularly *E. coli* and *Klebsiella* species. *E. coli* is isolated in approximately 70% of cases and *Klebsiella* species in 10% of cases [79]. However, gram-positive bacteria are becoming more common as the cause of SBP [77].

25.4 Treatment

Patients with a PMNL count greater than or equal to 250 cells/mm^3 or those with PMNL counts less than 250 cells/mm^3 but with signs and symptoms of infection should be administered empiric antibiotic therapy to treat SBP [78]. Timely treatment is important because untreated SBP carries an acute mortality of 50% [79]. The gold standard antibiotic class is third-generation cephalosporins, mainly cefotaxime. Two grams intravenously every 8–12 h for 5–10 days is recommended [77–79], and this has been shown to successfully treat 75–90% of cases of SBP [79]. Albumin, 1.5 g/kg intravenously within 6 h of detection and 1 g/kg on day 3, is added to this regimen to reduce the incidence of renal impairment and improve short-term survival [77–79]. Oral ofloxacin, 400 mg twice daily, is an effective alternative in patients without severe hepatic encephalopathy, vomiting, shock, and a creatinine level greater than 3 mg/dL [78].

The recurrence of SBP is 40–70% within 1 year [77, 79]. Therefore, after an episode of SBP, patients should receive long-term prophylaxis with norfloxacin,

400 mg orally daily, or trimethoprim–sulfamethoxazole (TMP–SMX), one single strength tablet daily. Those with gastrointestinal hemorrhage should receive norfloxacin, 400 mg twice daily, or TMP–SMX, one single strength tablet twice daily, for a total of 7 days as short-term prophylaxis [78].

Fluoroquinolone resistance has been increasing among gram-negative bacteria. This is contributed to long-term prophylaxis with norfloxacin. Resistance to TMP–SMX has also become a growing concern. This can possibly be counteracted by rotating antibiotics or by restricting the use of prophylaxis to those with the highest risk of developing a recurrence of SBP [79].

Key Points

- *C. albicans* is the most common cause of oral and esophageal fungal infections. It more commonly presents in immunocompromised individuals and can be treated with a variety of antifungal agents.
- *H. pylori* is a common, but treatable, cause of peptic ulcer disease.
- Acute diarrhea has a myriad of causes that can be differentiated by obtaining a detailed history, including travel history and recent medication use. Prevention is the key to avoiding acute diarrhea.

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Endocarditis

Eric Matheson

1 Introduction

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 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.

2 Clinical Description

Infective endocarditis 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 choose appropriate empiric therapy. Right-sided IE occurs in only 5–10% of patients with IE. Intravenous drug abusers (IVDAs) comprise the majority of these patients, and the prevalence of right-sided IE in these patients is 30 times that of the general population. Interestingly, 5–10% of patients with right-sided IE are not IVDAs [2, 3]. Among non-IVDA patients, hospitalization appears to increase the risk of right-sided IE. 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 predispose high-risk patients (those with underlying

E. Matheson (✉)
Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: matheson@musc.edu

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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 the 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 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 include neurological 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. Immune complex formation and deposition occurs predominately in the kidney, spleen, and skin [16]. The clinical presentation may be dominated by isolated immunological response 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 *Staphylococcus aureus, Candida* spp., and the HAECK 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 for diagnosing IE, as they may also be present in a variety of other diseases.

The Duke criteria for diagnosis of IE classify patients suspected of having IE into three categories based on the presence of specific pathological and clinical criteria [9, 19] (Table 1). Definitive IE requires the culture or histological demonstration of microorganisms in a vegetation or an intracardiac abscess or histological evidence of endocarditis in a vegetation or an 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 definitive IE are lacking but the diagnosis cannot be rejected, the patient is considered to have possible IE. The

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 the 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 the 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°C
3. *Vascular phenomena*: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. *Immunological 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 [19].

diagnosis is rejected when there is a resolution of clinical manifestations within 4 days of antibiotics, when there is no pathological evidence of disease after at least 4 days of antibiotics, or when there is a firm alternative 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 HAECK 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 [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 does 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 risk of IE is intermediate or high, in patients who are difficult to image, and in patients with high risk of complications [25].

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 days after an initial negative test [9]. In patients who have undergone both TTE and TEE, the negative predictive value is 95% [10].

2.1 Etiology

The most commonly encountered pathogens in bacterial IE are streptococci, staphylococci, and enterococci. The HAECK organisms (*Haemophilus* spp., *Actinobacter* spp., *Cardiobacterium* spp., *Eikenella* spp.) and gram-negative bacteria (*Klebsiella*

spp., *Pseudomonas* spp., and *Escherichia* spp.) are less frequently offenders. Other rare but important pathogens include *Rickettsia* spp., *Bartonella* spp., *Legionella* spp., *Brucella* spp., *Neisseria* spp., *Mycobacterium* spp., fungi, and *Norcardia* spp. These unusual organisms as well as members of the HAECK group are responsible for the majority of culture-negative endocarditis [1, 7–9, 26].

Staphylococcus aureus is the predominant pathogen in right-sided IE, both in IVDAs and other patients. *Candida* spp. have also been implicated as etiological agents in both groups of patients. gram-negative IE occurs more frequently in IVDAs [2, 4, 7, 9]. In contrast, left-sided valvular structures are most often targeted by streptococci, especially *S. viridans*. *Staphylococcus 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. More than 60,000 patients receive a prosthetic heart valve each year, and 3–6% ultimately develop IE [26]. Early PVE, occurring within the first 60 days 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, 27, 28]. The mortality rate of PVE is higher than that of native valve IE [2, 7, 28].

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, *S. bovis* often results in heart failure, necessitating 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 [29–31]. *Staphylococcus lugdunensis* is a highly virulent coagulase-negative organism causing approximately 1% of cases of acute IE [32]. Metastatic seeding, perivalvular seeding with abscess formation, and rapid valve destruction frequently occur despite appropriate antibiotic therapy [9, 33].

With each passing year, antibiotic-resistant organisms are responsible for a larger and larger number of IE cases. The pathogens that have been particularly problematic are *S. aureus, S. pneumoniae, Enterococcus spp*., and *Candida* spp. Rates of penicillin-resistant pneumococci have decreased somewhat in recent years but remain high at approximately 25% in most regions of the United States [34]. Although pneumococci are not a predominant cause of IE, mortality associated with infection is high [35].

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 increasing at an alarming rate, with resistance rates above 30% [36]. Methicillin-resistant *S. aureus* (MRSA) IE is most commonly seen in IVDAs and in hospitalized patients, although cases of community-acquired MRSA IE have become increasingly common, accounting for approximately 21% of cases [36–38].

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 the 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, 39].

2.2 Antimicrobial Therapy

Antibiotics for the treatment of infective endocarditis should be bactericidal and directed against the microorganism cultured from the blood. IVDAs and other patients with community-acquired infection may present with acute infective endocarditis. 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 ampicillin–sulbactam is recommended in patients with acute IE because *S. aureus* is the most common offending pathogen [2, 40]. Patients already on antibiotics, patients in whom infection with MRSA is suspected, patients with PVE (high likelihood of *S. epidermidis*), and patients with beta-lactam allergy should be treated with a combination regimen of vancomycin plus gentamicin, plus ciprofloxacin [40].

Table 2 Current recommendation for the treatment of SBE

Microorganism	Primary treatment	Alternative treatment
Streptococci PCN sensitive Native valve	PCN G (12–18 MU/d) × 4 week OR PCN G (12–18 MU/d) Plus gentamicin (3 mg/kg/d) × 2 weeks	Ceftriaxone (2 g/d) × 4 week OR Ceftriaxone (2 g/d) plus gentamicin (3 mg/kg/d) × 2 weeks OR Vancomycin (30 mg/kg/d) × 4 weeks
PCN-resistant native valve and prosthetic valve	PCN G (24 MU/d) × 4 week plus gentamicin (3 mg/kg/d) × 2 weeks	Ceftriaxone (2 g/d) × 4 weeks plus gentamicin (3 mg/kg/d) × 2 weeks OR Vancomycin (30 mg/kg/d) × 4 weeks
Staphylococci Methicillin sensitive	Nafcillin (12 g/d) × 6 week plus gentamicin (3 mg/kg/d) × 3–5 days	Cefazolin (6 g/d) × 6 weeks plus gentamicin (3 mg/kg/d) × 3–5 days
Prosthetic valve	Nafcillin (12 g/d) × 6 weeks plus rifampin (900 mg/d) × 6 weeks plus gentamicin (3 mg/kg/d) × 2 weeks	
Methicillin resistant Native valve	Vancomycin (30 mg/kg/d) × 4–6 weeks	
Prosthetic valve	Vancomycin (30 mg/kg/d) × 6 weeks plus rifampin (900 mg/d) × 6 weeks plus gentamicin (3 mg/kg/d) × 2 weeks	

Table 2 (continued)

Microorganism	Primary treatment	Alternative treatment
Enterococci (native or prosthetic valve) PCN sensitive	PCN G (18–30 MU/d) × 4–6 weeks plus gentamicin (3 mg/kg/d) × 4–6 weeks	Ampicillin (12 g/d) plus gentamicin (3 mg/kg/d) × 4–6 weeks OR Vancomycin (30 mg/kg/d) × 6 weeks plus gentamicin (3 mg/kg/d) × 6 weeks
Vancomycin resistant	Linezolid (1200 mg/d)	
HACEK group (native or prosthetic valve)	Ceftriaxone (1 g/d) × 4 weeks	Ampicillin–sulbactam(12 g/d) plus gentamicin (3 mg/kg/d) × 4–6 weeks OR Vancomycin (30 mg/kg/d) × 6 weeks plus gentamicin (3 mg/kg/d) × 6 weeks

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The treatment of subacute bacterial endocarditis differs from that of acute infective endocarditis 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 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.

3 Antimicrobial Therapy of Resistant Organisms

With the rapid proliferation of antibiotic-resistant pathogens in recent years, the treatment of endocarditis has become increasingly difficult. Treatment is particularly difficult in the case of antibiotic-resistant *S. aureus,* which now accounts for at least 10% of all cases of endocarditis [41, 42]. While the standard of care for treatment is vancomycin, the failure rate remains high at nearly 20% [31]. One potential alternative to vancomycin is linezolid, which has been shown to be effective in rabbit models [43]. However, human trials with linezolid are lacking, so treatment with linezolid should be used only with great caution. More recently, daptomycin has been approved by the Food and Drug Administration for treatment of right-sided endocarditis based on a study which demonstrated similar if not better efficacy than vancomycin [44]. Finally, tigecycline has demonstrated good efficacy against MRSA in rat models of IE, but human trials are lacking, so this medication should be

used only if other choices fail [45]. Several medications currently being investigated which show promise include dalbavancin, telavancin, oritavancin, and ceftobiprole [42].

Enterococci have become increasingly resistant to current therapy, and aminoglycoside adjuvant therapy is becoming less efficacious. Most troubling is the rapidly increasing resistance to vancomycin. The seriousness of the 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 develop enterococcal infections, especially those patients with VRE [8, 39].

Patients with beta-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 [46].

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–sulbactam in combination with an aminoglycoside [39]. In the presence of VRE highly resistant to ampicillin, no reliable bactericidal regimen is currently available. However, case reports show some success with linezolid [47]. In addition, some institutions are using other antibiotics including quinupristin/dalfopristin, daptomycin, and tigecycline but data on the efficacy of such treatment is lacking [48].

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 infection caused by beta-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 [39]. Health-care providers have an obligation to both educate themselves regarding the appropriate use of antibiotics and comply with current guidelines outlining the appropriate use of antimicrobial agents.

3.1 Surgical Therapy

Surgery is an important adjunct to antibiotics in treating patients with IE. In fact, surgery is needed in nearly half of all cases of IE [49]. A primary indication for surgery is the presence of progressively worsening or refractory congestive heart failure (CHF) [50]. Valve replacement or repair is recommended early in the course

of CHF, as rates of morbidity and mortality are lower at this time [51]. In fact, delaying surgery in CHF patients until severe ventricular dysfunction develops nearly doubles the rate of mortality [1, 9, 52, 53].

Combined medical and surgical treatment is clearly superior to medical treatment alone in patients with cardiac complication, prosthetic valve endocarditis, and IE with resistant microorganisms [50]. 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 with only antibiotics [28, 52, 54]. 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 [54].

The size of valvular vegetations and subsequent embolic phenomena are also important factors in determining the need for and timing of surgery. 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, then surgery should be considered [9, 47, 52].

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, surgery is generally recommended regardless of vegetation size [40, 55]. Surgery 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 the likelihood of systemic embolization is higher and in patients with other predictors of post-IE complications [9, 49, 54].

Other indications for which adjunctive surgery should be considered are the following: (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 options in patient with IE due to fungal or other highly resistant organisms for which medical therapy alone is limited [1, 9, 28, 37, 40, 52, 53].

3.2 Antibiotic Prophylaxis

Given the increasing incidence of IE among certain segments of the population, the medical community has focused intensely on primary prevention as a means for reducing morbidity and mortality. Historically, the American Heart Association has recommended antibiotic prophylaxis prior to a wide variety of surgical and dental procedures for patients with structural heart disease to prevent IE [56]. In 2007, the American Heart Association Guidelines for antibiotic prophylaxis changed, significantly reducing the number of patients who need antibiotic prophylaxis [57]. These changes resulted from a series of case–control studies, suggesting that antibiotic prophylaxis does little to reduce the risk of IE and is associated with noteworthy iatrogenic complications [47]. Table 3 outlines the current conditions for

Table 3 Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous IE
Congenital heart disease (CHD)[a]
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure[b]
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or a prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

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[a]Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

[b]Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

which antibiotic prophylaxis is recommended, and Table 4 outlines the appropriate antibiotic dosing.

Antibiotic prophylaxis is reasonable for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Table 3). Antibiotic prophylaxis solely to prevent IE is not recommended for genitourinary or gastrointestinal tract procedures.

Table 4 Regimens for a dental procedure

Situation	Agent	Regimen: Single dose 30–60 min before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin[a,b] OR	2 g	50 mg/kg
	Clindamycin OR	600 mg	20 mg/kg
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[b] OR	1 g IM or IV	50 mg/kg IM or IV
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

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IM, intramuscular; IV, intravenous.

[a]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

4 Fungal Endocarditis

Fungal endocarditis (FE) is rare and predominately occurs in hospitalized patients, in immunocompromised patients, in patients with prosthetic valves, or IVDAs [58–61]. *Candida* spp. and *Aspergillus* spp. cause the majority of FE; however, other non-*albicans Candida, Cryptococcus* spp., *Histoplasma* spp., and *Coccidiomyces* spp. may be etiologic [59, 61]. Despite available antifungal therapy, mortality remains greater than 50% [62]. Factors predisposing patients to the development of FE include prosthetic cardiac devices, widespread and prolonged use of antibiotics, invasive diagnostic procedures, previous bacterial endocarditis (BE), chemotherapy, and open heart surgery [58–62].

There are no characteristic clinical features of FE that distinguish it from BE. Fever, constitutional symptoms, splenomegaly, and neurological complications may be observed in both FE and BE. Massive and fatal embolization to more deep-seated organs (i.e., brain, mesentery, and heart) occurs with greater frequency in FE than in BE, 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 reveal large vegetations which are usually left-sided and may be non-valvular. Diagnosis is often made by biopsy or surgical removal of a systemic embolus [58–60, 62].

The current recommendation for the treatment of FE is surgical replacement of the involved valves with adjunctive antifungal therapy [25, 58, and 60]. Amphotericin B (AmB) is the antifungal agent of first choice, and many advocate the concomitant use of flucytosine and rifampin as synergist agents. Due to the high failure rate of current therapy, some practitioners use fluconazole, itraconazole, and voriconazole; however, these medications appear no more effective than traditional therapy. The optimal dose of antifungal therapy and the duration of therapy are not clearly defined. A dose of 2.5–5 mg/kg/d of the liposomal preparation of amphotericin B (AmB) for at least 6 weeks 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 does the non-liposomal preparation [58, 60].

Despite the inherent role of surgery in treating FE, additional foci of infection often persist, resulting in reinfection of 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 [59–61].

The problem of antibiotic 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 develop resistant FE, particularly fluconazole monotherapy and prophylaxis [59, 63]. 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 [63].

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 also to AmB after azole therapy. It has been postulated that exposure to fluconazole results in the depletion of the fungal membrane ergosterol content, resulting in resistance to AmB [63]. Several new antifungal agents are being examined for potential use in the treatment of FE. One group consists of the β-1,3-glucan synthase inhibitors caspofungin, micafungin, anidulafungin, which are used in the treatment of *Candida* spp. Another group consists of the second-generation triazoles which include voriconazole, posaconazole, and ravuconazole, which are effective against a broad range of fungal infections [63–65]. Unfortunately, in spite of the recent advances in antifungal agents, the optimum treatment for fungal endocarditis remains unclear.

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 of fungi.

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Infections of the Central Nervous System

Nicoline Schiess and Avindra Nath

1 Introduction

Infections of the central nervous system (CNS) cause a major health and economic toll on society, due to the significant morbidity and mortality associated with these infections. Proper recognition and early treatment can have a notable and positive impact on the outcome of most of these infections.

2 Acute Meningitis

The presentation of acute meningitis is dramatic, with clinical manifestations commonly developing over only a few hours to days. Typical presenting symptoms are high fever, headache, photophobia, stiff neck, and altered mental state. Headache and vomiting, due to raised intracranial pressure, may be an early manifestation, particularly in young children. Infants, immune-suppressed individuals, and the elderly may not develop neck stiffness, thus lacking this cardinal sign of meningeal irritation.

2.1 Etiology

The leading causes of acute meningitis are viruses and bacteria. The most feared of all is meningococcal meningitis. The presence of purpura or petechial rash on the trunk, lower extremities, and mucous membranes, including conjunctiva, but the absence in the nail beds, is highly suggestive of meningococcemia. Patients with fulminant meningococcal septicemia may develop the Waterhouse–Friderichsen

N. Schiess (✉)
Division of Neuroimmunology and Neuroinfectious Disease, Johns Hopkins Department of Neurology, Baltimore, MD, USA
e-mail: nschies1@jhmi.edu

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syndrome, characterized by cardiovascular collapse associated with hypoadrenalism and disseminated intravascular coagulation.

The leading cause of acute bacterial meningitis in children is *Haemophilus influenzae*; however, its incidence has dramatically decreased following the introduction of an effective vaccine. *H. influenzae* meningitis in children is frequently associated with epiglottis 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 trauma or cerebrospinal fluid (CSF) leaks, and alcoholism. Pneumococci are also the most common cause of meningitis in children with sickle cell anemia and other asplenic states. Asplenic patients are predisposed to pneumococcal disease because they are unable to mount an antibody response.

Listeria monocytogenes is an important cause of neonatal meningitis and is transmitted via the maternal genital tract during delivery. Diabetics, renal transplant patients, alcoholics, the elderly, and sometimes other individuals may also develop *Listeria* meningitis after ingestion of contaminated (usually unpasteurized) food. *Listeria* causes a rhombencephalitis in about 10% of listeriosis cases [1], affecting predominantly the posterior fossa structures.

Patients with neutropenia are at particular risk for meningitis due to *Pseudomonas aeruginosa* and other enterobacteria. Because these patients are unable to mount an effective inflammatory response, they may have minimal meningeal symptoms despite serious infection.

The most common causes of viral meningitis are enteroviruses followed by arboviruses. However, establishing the exact viral etiology is often of little clinical importance, because no specific treatment is currently available for these viruses, with the exception of HIV infection. HIV may present with an aseptic meningitis during the acute state of illness.

It is important for the clinician to differentiate infectious meningitis from the non-infectious causes of acute meningitis, including systemic lupus erythematosus, rare reactions to non-steroidal anti-inflammatory drugs, and Behcet's syndrome. Mollaret's meningitis is of uncertain etiology, but herpes simplex virus-2 has been implicated in some cases [2].

2.2 Laboratory Diagnosis

In a patient with suspected meningitis, it is urgent to establish the diagnosis by a CSF evaluation, because treatment delay is the most critical factor in determining morbidity and mortality from bacterial meningitis. Nevertheless, it has become common practice to obtain a computed tomographic (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, where 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 and

should be performed without first obtaining a CT or an MRI scan. Following the lumbar puncture, antimicrobial therapy should be started promptly, pending results. In cases where antibiotics were given prior to the lumbar puncture, the puncture may be done after starting antibiotics, as antibiotics take about 24 h to sterilize the CSF.

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 with a decrease in glucose in the CSF.

2.3 Treatment of Bacterial Meningitis

2.3.1 Empirical Therapy of Community-Acquired Bacterial Meningitis

Adults

The most common organism causing bacterial meningitis in adults is *S. pneumoniae*. However, an increasing number of strains are resistant to penicillin, and some strains are resistant to third-generation cephalosporins. Cephalosporin-resistant strains are more frequent in children than in adults [3]. For relatively penicillin-resistant strains (minimal inhibitory concentration 0.1–1.0 μg/ml), a third-generation cephalosporin (e.g., 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 combination of choice. Recommended drug therapies for meningitis, due to other organisms, are summarized in Table 1. Patients with neutropenia and meningitis should be empirically treated with a third-generation cephalosporin (e.g., ceftazidime to provide *Pseudomonas* coverage) and vancomycin, pending culture and sensitivity results.

Infants and Children

Antibiotic coverage for bacterial meningitis in children should be effective against *H. influenzae, S. pneumoniae, and Neisseria meningitidis.* Thus, a third-generation cephalosporin (ceftriaxone or cefotaxime) and vancomycin are recommended as initial therapy. Cefuroxime, also a third-generation cephalosporin, should be avoided in children because of reports of delayed sterilization of the CSF and an association with hearing loss in children when this drug was used.

Neonates

Antibiotic coverage chosen to treat bacterial meningitis in neonates should be effective against group B streptococci, *Escherichia coli*, and *L. monocytogenes*. Thus, therapy should include ampicillin and also cefotaxime or an aminoglycoside.

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	
Highly resistant to penicillin	Vancomycin plus Cefotaxime or ceftriaxone	
Highly resistant to cephalosporins	Vancomycin plus rifampicin	
Neisseria meningitidis	Penicillin G or Ampicillin	Ceftriaxone or cefotaxime for penicillin-resistant strains Rifampin, minocycline, or ciprofloxacin for close contacts of index case
Gram-negative bacilli (except *P. aeruginosa*)	Ceftriaxone or cefotaxime	
P. aeruginosa	Ceftazidime	May add aminoglycoside in the first week of treatment
L. monocytogenes	Ampicillin	Cephalosporins are inactive
Staphylococcus	Nafcillin	
Methicillin-resistant staphylococcus	Vancomycin	May add rifampicin
Streptococcus agalactiae	Ampicillin or penicillin	
H. influenzae	Cefotaxime or ceftriaxone	Increasingly strains are resistant to ampicillin or chloramphenicol or both
Enterobacteriaceae	Cefotaxime or ceftriaxone	

Other Categories of Patients

The neutropenic patient should be treated with antibiotics effective against *Pseudomonas*, *Staphylococcus*, and *Listeria*. Asplenic patients should be covered for *S. pneumonia* and *H. influenzae*. Older adults (>50 years of age) should be treated with a third generation cephalosporin (ceftriaxone or cefotaxime) in combination with ampicillin to provide coverage for *S. pneumoniae, E. coli, Listeria*, and *H. influenzae*.

2.3.2 Adjunctive Steroid Therapy

The role of steroids in meningitis has been controversial over the last two decades. Currently, the recommendations of the American Academy of Pediatrics are that in the setting of *H. influenzae* b meningitis, the use of steroids may be beneficial if given before or within 1 h of antimicrobial therapy. However, in other

cases, including pneumococcal or meningococcal meningitis, the decision should be individualized and the risk/benefit ratio weighed [4].

3 Subacute or Chronic Meningitis

Subacute or chronic meningitis is characterized by a gradual onset. These syndromes may persist for weeks, months, or years. The clinical signs can include headache, fever, stiff neck, and altered consciousness. Lower cranial nerve palsies may accompany basilar meningitis.

3.1 Etiology

Lyme disease is due to infection with *Borrelia burgdorferi*, and nervous system involvement usually presents as a chronic meningitis. CNS involvement should be suspected if a combination of facial nerve palsy (often bilateral) and aseptic meningitis is present. Later in the course, the disease may manifest as 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 a secondary annular skin lesion. Other symptoms may include myalgias, arthralgias, dysesthesias, or abdominal pain.

Fungal meningitis occurs primarily in immunosuppressed individuals. *Cryptococcus neoformans* is the most common cause of meningitis in patients with HIV infection and in transplant patients. Other fungal infections that may occur in individuals with defects in cell-mediated immunity include coccidioidomycosis and histoplasmosis. Patients with granulocytopenia are at risk of developing infections due to *Candida*, *Aspergillus fumigatus*, and *Zygomycetes* organisms (mucormycosis).

Tuberculous meningitis may occur in non-immunosuppressed hosts as well as in HIV-infected patients. Patients with HIV are more likely to have symptoms suggestive of extrameningeal tuberculosis.

Treponema pallidum is a spirochete that causes syphilis. It is now recognized that CNS disease can occur through all stages of infection. Several well-characterized CNS syndromes have been described with *T. pallidum* and can be broadly classified into those with meningeal involvement (asymptomatic, subacute meningitis, meningovascular syphilis), which occur early and are common, and those with parenchymal involvement (general paresis, tabes dorsalis, and gumma), which occur several years after the primary infection and are rare. In contrast to the pre-antibiotic era, neurosyphilis today is identified in young patients most often with HIV co-infection, and early symptomatic syndromes and asymptomatic neurosyphilis are identified more frequently than late neurosyphilis syndromes.

Important non-infectious causes of subacute or chronic meningitis include the following: sarcoidosis, systemic lupus erythematosus, vasculitides, carcinomatous meningitis, and Vogt–Koyanagi–Harada syndrome.

One disease entity to also keep in mind when an HIV-infected patient presents with a subacute meningoencephalitis is the immune reconstitution inflammatory syndrome (IRIS). IRIS clinically presents as an unexpected, symptomatic deterioration in HIV-infected patients weeks or months after starting highly active antiretroviral therapy (HAART) when the patient is showing an improvement in viral load and CD4 cells counts. It occurs secondary to the recovery of the immune system from HAART with subsequent immune assault on the central nervous system.

3.2 Laboratory Diagnosis

Fungal meningitis is most common among immunosuppressed patients and is also often associated with thrombocytopenia. With this in mind, platelet counts should be performed prior to performing a lumbar puncture. Neuroimaging (CT or MRI scan), preferably with contrast, should also be performed in these patients because 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 LP is performed. If repeated cultures are negative and it remains essential to establish a diagnosis, then a cisternal puncture may be considered. Biopsy of the basilar meninges may also be performed, but it carries a high morbidity rate. Biopsies of the cortical meninges are typically negative and thus not very practical. For *Cryptococcus* species, 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% of patients [5].

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 days), polymorphonuclear cells may be present, which later get replaced by lymphocytes. Following initiation of antituberculous therapy, polymorphonuclear cells may reappear in the CSF. Cultures require 3–6 weeks and are positive in about 75% of patients.

Two types of serological tests are available for diagnosing syphilis, treponemal, and non-treponemal tests. A large number of conditions have been described in which false-positive syphilis serologies may occur. Most experts recommend a newly reactive positive CSF VDRL as a criterion for diagnosing asymptomatic neurosyphilis.

For diagnosis of Lyme disease, positive or equivocal results on an ELISA, an IFA, or an immunodot assay require supplemental testing with a Western blot assay. A negative result on the Western blot or the ELISA indicates that there is no serologic evidence of infection by *B. burgdorferi*.

While polymerase chain reaction (PCR) has revolutionized clinical diagnoses for several central nervous system infections, particularly viral and some bacterial infections, it has not turned out to be particularly useful in the diagnosis of fungal infections or for spirochetes despite its extreme sensitivity [6, 7].

3.3 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 frequently, typically every other day for the first month and then weekly for the duration of therapy. Adding flucytosine allows the dose of amphotericin B to be reduced and thus decreases the chance of developing nephrotoxicity. However, at serum flucytosine concentrations of >100 μg/ml, bone marrow suppression may occur. For this reason, drug levels should be monitored regularly. The risk of bone marrow suppression should be carefully weighed in patients with 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 [8].

3.3.1 Coccidial Meningitis

Treatment of coccidial meningitis requires the use of intravenous and intrathecal amphotericin B or oral azole antifungal drugs such as fluconazole. Amphotericin B may be administered via an Ommaya reservoir. Patients may have to be treated indefinitely.

3.3.2 Cryptococcal Meningitis

In one clinical trial, non-AIDS patients treated with amphotericin B plus fluconazole required 36% fewer days of hospitalization than those receiving amphotericin B alone [9]. In non-AIDS patients, a negative or low cryptococcal antigen titer suggests that the infection is adequately treated. However, in AIDS patients, CSF cryptococcal antigen may remain positive despite adequate treatment due to the release of antigen from dead cells or slow clearing of the antigen from the CSF. Hence, clinical status is the best indicator for therapy response 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. Poor prognostic factors, in AIDS patients, include high titer of cryptococcal antigen in CSF, low serum albumin level, and low CD4 cell count. Together with subtherapeutic doses of amphotericin B, these prognostic factors are strongly associated with failure to achieve negative CSF cultures after 2 weeks of treatment [10].

3.3.3 Tuberculous Meningitis

Initiation of empiric chemotherapy should not await the results of CSF cultures. Isoniazid and pyrazinamide have excellent penetration of the blood–CSF and of the blood–brain barriers even under non-inflamed conditions and, hence, form the backbone of all anti-tuberculosis therapy. In non-AIDS patients, treatment of

tuberculous meningitis should be initiated with isoniazid, rifampicin, and pyrazinamide. Pyridoxine is given to prevent isoniazid-induced peripheral neuropathy. When antimicrobial resistance is suspected, ethambutol may also be added. Once a clinical response is noted, and sensitivity confirmed, pyrazinamide and ethambutol may be discontinued (usually after 2 months of treatment). Isoniazid and rifampicin should be continued for 9–12 months. Patients suspected of having possible resistant tuberculosis should be referred to a specialist for management.

In patients with HIV infection, it is recommended that treatment of tuberculous meningitis be initiated with four drugs: isoniazid, rifampicin, either ethambutol or pyrazinamide as the third drug, and either streptomycin, rifabutin, or clofazimine as the fourth drug [11]. The dosage for isoniazid is two to three times that of non-AIDS patients (i.e., 10–15 mg/kg/day). For this reason, AIDS 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.

For HIV-negative children with tuberculous meningitis, the American Academy of Pediatrics recommends the use of isoniazid, rifampicin, pyrazinamide, and streptomycin for 2 months followed by isoniazid and rifampicin for another 10 months [12]. They recommend that liver function be monitored for the first several months. For children with HIV and tuberculous meningitis, the ideal drug regimen is still uncertain, though the Academy also recommends that the use of corticosteroids be considered in this patient population; steroids decrease cerebral edema and the inflammatory reaction, which, in and of itself, can cause damage [13]. In these children, consultation with a specialist is indicated.

3.3.4 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 days [14]. 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 days [14].

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. Higher dosages of penicillin given for 10–14 days offer no clear advantage over benzathine penicillin [15]. Careful observation coupled with a low threshold for repeat CSF evaluation remains the recommended management strategy for these patients [16].

In patients allergic to penicillin, suggested alternatives include tetracyclines, chloramphenicol, and ceftriaxone; however, use of these alternatives in the HIV population has not been extensively studied and should be used with caution.

3.3.5 Lyme Disease

Intravenous ceftriaxone (2 g IV daily) or cefotaxime (2 g IV every 8 h) is the treatment of choice for nervous system involvement with Lyme disease, due to their strong CSF penetration and long half-life [17, 18]. However, controlled trials have shown that intravenous penicillin [17] and doxycycline may be just as effective [19, 20]. For all of the above regimens, the American Academy of Neurology's recommended duration of therapy is 14 days, though the duration in studies has varied from 10 to 28 days [21] (see Table 2).

Table 2 AAN practice guidelines for the treatment of CNS Lyme disease [29]

1. Parenteral ceftriaxone, cefotaxime, and penicillin are safe and effective treatment options
2. Oral doxycycline is a reasonable alternative for CNS Lyme disease not involving the brain parenchyma
3. Prolonged courses of the above antibiotics *do not* improve outcome and can be associated with adverse events. They are therefore *not recommended*

4 Acute Encephalitis

When encephalitis develops, 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 myoclonus or tremor. Acute viral encephalitis almost always is accompanied by a fever; however, hypothalamic involvement may lead to hyperthermia or hypothermia, autonomic dysfunction with vasomotor instability, or diabetes insipidus. Spinal cord infection is usually inconspicuous but can result in flaccid weakness, with acute loss of reflexes in the most severe cases.

4.1 Etiology

Herpes simplex virus type 1 (HSV) encephalitis is the most common identified cause of severe, sporadic viral encephalitis in the United States. Although immunological mechanisms are important in HSV latency and its peripheral reactivation, HSV encephalitis usually occurs in immunocompetent hosts and does not appear to be related to immunosuppression. The infection commonly involves the frontal and temporal lobes, so seizures with fever are a common initial manifestation.

Other viruses that cause encephalitis include cytomegalovirus virus (CMV), varicella zoster virus (VZV), and West Nile virus (WNV). CMV encephalitis can result 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 CMV ventriculitis. Nearly all patients with CMV encephalitis have systemic CMV infection.

Varicella zoster virus (VZV) encephalitis in HIV-infected patients may present as stroke-like syndromes and a retinitis, due to a vasculopathy caused by the virus.

In 1999, West Nile virus (WNV) was introduced into New York City and has subsequently spread to all continental US states except Maine. WNV, a type of flavivirus, is now the most widely distributed arbovirus on the globe; its spread is most likely due to migratory birds and mosquitoes [22]. Other arboviruses such as Saint Louis, Western equine, and Eastern equine viruses also cause encephalitis in the United States but vary in their geographical distribution.

Mumps and lymphocytic choriomeningitis virus are among the less common causes of viral encephalitis. Rabies results in a devastating and nearly invariably fatal encephalitis. Viral transmission characteristically results from the bite of a rabid animal, although in cases involving bats, the patient is often unaware of a bite. The interval between the bite and the onset of disease in most cases is 1–2 months. This delay affords an opportunity for prophylactic post-exposure immunization after the bite. Once the virus enters peripheral and central nervous system pathways, immune defenses are unable to suppress further replication and spread of infection. 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. As the disease progresses from the paralytic form to the encephalitic form, patients succumb to respiratory failure or cardiovascular collapse. Intensive supportive care may extend survival in rare cases.

4.2 Laboratory Diagnosis

When evaluating a patient suspected of encephalitis, neuroimaging with head CT scanning or cranial MRI is generally the initial diagnostic measure. The MRI is significantly more sensitive and often reveals highly characteristic abnormalities. Heavy sedation or even general anesthesia may sometimes be required to perform the MRI, due to agitation and inability to cooperate with the study. The MRI is also sensitive in suggesting other similar presenting pathologies such as brain abscess, vasculitis, or demyelination. In the case of HSV encephalitis, MRI may show virtually pathognomonic increased signal abnormalities on T2-weighted sequences in the medial temporal, insular cortical regions, and inferior frontal cingulate gyri in patients.

In patients with CMV encephalitis, MRI may show ependymal or meningeal enhancement and 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 because other viral CNS infections cause a lymphocytosis in the CSF.

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.

Although reports on MRI findings in patients with rabies are limited, the MRI can show T2 hyperintense lesions in the brainstem, thalami, hippocampus, and subcortical white matter. Gadolinium post-contrast enhancement is not present until the patient is comatose.

4.3 Treatment

Effective antiviral therapy is available against HSV, CMV, and varicella; the latter two generally cause encephalitis in immune-compromised patients, while HSV is not linked to immunosuppression [23]. In immunocompromised patients, long-term therapy may be necessary; however, the length of treatment should be determined on a case-by-case basis. Treatment of acute viral encephalitis other than the herpes viruses or HIV 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 stool and 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.

HSV encephalitis should be considered a medical emergency, due to its characteristically aggressive course, and antiviral therapy with intravenous acyclovir should be administered at the time the diagnosis is considered. Drug excretion is through the kidney, and thus acyclovir should be administered cautiously in patients with impaired renal function. If the diagnosis subsequently cannot be confirmed, then acyclovir can be safely discontinued. Cases of resistance to acyclovir have been reported, typically in immunocompromised patients. In HSV encephalitis patients whose virus is resistant to acyclovir, foscarnet or cidofovir can be used.

CMV- and VZV-related encephalitis should be treated with ganciclovir or foscarnet; however, the evidence of the drugs' 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.

In the case of possible exposure to a rabid animal, the decision to vaccinate depends on the type of possible exposure: an open wound or a 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 thorough washing with soap and water, then application of 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. Current tissue culture-derived vaccines have a low incidence of adverse reactions in contrast to earlier vaccines. Supportive treatment of rabies has been the standard of care; however, the one reported survivor in the literature was treated with induction of coma (Willoughby, 2005 #17).

4.3.1 Symptomatic Management of Encephalitis

Headache and fever 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. Even in cases with severe manifestations, some patients may achieve remarkable recovery if provided vigorous supportive therapy. Meticulous care in an intensive care unit setting with respiratory and nutritional support is justified. Although seizures sometimes complicate encephalitis, prophylactic anticonvulsants are not routinely recommended. If status epilepticus ensues, then appropriate therapy should be instituted to prevent secondary brain injury and hypoxia.

Generally, steroids should probably be avoided in the treatment of encephalitis because they inhibit host immune responses. There are no controlled studies on the use of steroids in patients with viral encephalitis. However, in the presence of significant cerebral edema with impending brain herniation, high-dose corticosteroid therapy (4–6 mg dexamethasone every 4–6 h) should be considered. While 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.

4.4 Prognosis

The prognosis of encephalitis depends on its cause. Arbovirus encephalitides have variable mortality rates. Eastern equine encephalitis has the highest mortality rate of all arboviruses, while California virus has the lowest. The mortality rates for most viral encephalitides are greater in children under 4 years of age and in the elderly. Non-fatal encephalitis caused by Eastern equine, Western equine, West Nile, and St. Louis viruses leaves a relatively high rate of neurologic sequelae. Encephalitis associated with mumps or lymphocytic choriomeningitis 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 initiation of therapy determine the outcome. Relapse has been observed in rare patients despite seemingly adequate antiviral treatment. This relapse usually occurs within a few weeks of the resolution of the acute illness and often results in severe sequelae.

5 Chronic Encephalitis

5.1 Etiology

Most chronic encephalitis syndromes have characteristic neurological manifestations that help distinguish them from each other. 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 functional categories: cognitive, motor, and behavioral. The primary cognitive symptom is forgetfulness, associated with impaired concentration and difficulty in reading. Lower extremity weakness and impaired balance are among the early motor signs. 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. Survival has improved since the introduction of HAART. Subtypes of HIV dementia have been defined in relation to their temporal course.

In patients with HIV infection, a new neurological syndrome called CNS-immune reconstitution inflammatory syndrome (CNS-IRIS) has emerged. These patients may develop a subacute progressive encephalitis that eventually results in coma and death, despite adequate treatment with antiretroviral drugs. Risk factors for development of CNS-IRIS include initiation of antiretroviral therapy in patients with low CD4 cells counts (<50 cells/mm^3), rapid drop in plasma viral load, and persistent HIV in CSF despite control in the peripheral blood. IRIS may also occur in patients with CNS opportunistic infections following initiation of antiretroviral therapy; these patients develop neurological deterioration due to enhanced inflammation as the cell-mediated immune response is reconstituted. Occasionally, the CNS opportunistic infection may manifest itself only after the initiation of antiretroviral therapy. In these patients, it is thought that either the pathogen is brought into the brain by the cellular components of the cell-mediated immune response or the lymphocytes release cytokines that activate latent reservoirs of the pathogen in the brain.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that occurs in immunosuppressed patients and is caused by JC virus, a papovavirus widely distributed among humans. PML is most commonly seen in the AIDS population. PML may also occur in patients on chemotherapeutic drugs for treatment of cancer, organ transplant, or autoimmune diseases. Recently, PML cases were reported in patients treated with natalizumab, which blocks T cell trafficking into the brain, and in patients treated with rituximab, an antibody to B cells.

Subacute sclerosing panencephalitis (SSPE) is caused by measles virus. Patients usually have a history of measles rash at <2 years of age, and it is speculated that such early host exposure allows the emergence of persistent defective virus replication. Due to an effective vaccination strategy against measles virus, the incidence of SSPE has markedly decreased in recent years. SSPE usually begins with cognitive and behavioral changes and progresses to include motor dysfunction with prominent myoclonus, choreoathetosis, dystonia, and rigidity. It usually causes a progressive deterioration over 1–3 years, eventually resulting in rigid quadriparesis and a vegetative state.

5.2 Laboratory Diagnosis

In a patient who presents with a clinical picture of chronic encephalitis, it is important to exclude non-infectious causes of dementia and other neurodegenerative diseases (see Table 3). 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 examinations in HIV-infected patients frequently show an elevated total protein, mild pleocytosis, increased total immunoglobulin fraction, and oligoclonal bands. Neuroimaging studies are generally nonspecific.

Table 3 Treatable, non-infectious 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

In patients with PML, 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. The CSF protein may be elevated and myelin basic protein may be detected. PCR for JC virus has sensitivity of 43–92% and specificity of 92–100%. In the United States, PCR for JC virus is now routinely used to establish the diagnosis of PML [24].

In SSPE, the electroencephalogram (EEG) shows periodic complexes with synchronous bursts of two or three slow waves per second, recurring at 5–8 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 the CSF 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.

5.3 Treatment

Treatment for HIV has evolved into a specialty of its own and is a rapidly changing and evolving field. Patients with HIV encephalitis and dementia are best referred to a specialist for management. The relative CSF penetration of antiretroviral drugs is provided in Table 4 [25].

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 that intrathecally and intravenously administered the drug in patients with AIDS-associated PML demonstrated no benefit [26]. Since the introduction

Table 4 Characteristics of antiretroviral drugs with high penetration into the CSF and most effective control of CSF viral load

Generic name	Drug class	Abbreviation	Common side effects (comments)
Zidovudine	Nucleoside reverse transcriptase (RT) inhibitor	AZT, ZDV	Bone marrow suppression, GI upset, headache, myopathy
Abacavir	Nucleoside RT inhibitor	ABC	GI upset, hypersensitivity reaction
Nevirapine	Non-nucleoside RT inhibitor	NVP	Rash
Indinavir/ritonavir	Protease inhibitor	IDV/RTV	Kidney stones, hyperbilirubinemia (take on an empty stomach)
Lopinavir/ritonavir	Protease inhibitor	LPV/RTV	Hepatitis, pancreatitis, increased triglycerides

of HAART, survival in AIDS-associated PML has appeared to improve [24]. Thus, immune reconstitution seems to be the best treatment for PML if it can be achieved. This can be particularly challenging in non-AIDS PML, especially in patients with cancer or organ transplants. There is no established treatment for SSPE, although case reports suggest that interferon with inosiplex may stabilize symptoms in some patients [27].

5.4 Prognosis

Prior to HAART, HIV dementia was typically rapidly progressive, with a mean survival of about 6 months, less than half the average survival of non-demented AIDS patients [28]. Occasionally, patients may remain mildly demented and cognitively stable until death. Similarly, CNS-IRIS also seems to have high morbidity and mortality rates if not recognized early.

PML usually progresses to death within a mean of 6 months. In approximately 9% of patients with AIDS-associated PML, survival may exceed 12 months, often with partial or nearly complete clinical and radiographic recovery.

SSPE has a dismal prognosis. Once patients become symptomatic, coma and death generally follow within a few years.

6 Space-Occupying Lesion Syndrome

Cerebral abscesses result in focal neurological deficits with specific manifestations dependent on the site of the lesion. Symptoms may include visual field deficits, focal seizures, aphasias, hemiparesis or hemisensory deficits, cranial nerve palsies,

or cerebellar dysfunction. Non-focal symptoms, such as a confused state or a personality disorder, may be an initial manifestation, but as the disease progresses, focal symptoms eventually appear. If multiple cerebral abscesses are present, then multifocal symptoms may result.

6.1 Etiology

Although a number of bacterial, fungal, and parasitic infections may cause cerebral abscesses, this section primarily discusses the management of cerebral toxoplasmosis, which since the emergence of HIV infection has become the most frequent cause of cerebral abscess. The causative agent of toxoplasmosis is a coccidian parasite *Toxoplasma gondii*. Cats serve as natural reservoirs of *Toxoplasma*, although virtually any animal that ingests material contaminated with oocytes can get infected. Clinical manifestations typically evolve over several weeks and include focal signs referable to the site of the abscess.

6.2 Diagnosis

Cerebral toxoplasmosis is the most likely diagnosis in an immunosuppressed patient who presents with focal neurological signs and multiple cerebral ring-enhancing lesions on neuroimaging. A lack of response to such therapy should alert the clinician about the possibility of other conditions, such as CNS lymphoma or progressive multifocal leukoencephalopathy. In patients with solitary lesions, the possibility of cerebral lymphoma is more likely. In patients who are seronegative for toxoplasmosis or are on prophylactic therapy for toxoplasmosis, other diagnoses should be considered.

PCR for *Toxoplasma* on CSF has a 100% specificity for documented or presumed encephalitis with a sensitivity of about 50%. Neuroimaging techniques demonstrate the abscesses usually as multiple ring-enhancing lesions with mass effect and surrounding edema. An MRI is more sensitive than a CT scan in demonstrating these lesions.

6.3 Treatment

The choice of drugs for treating cerebral toxoplasmosis is limited. Pyrimethamine and sulfonamide should be used in combination. Clindamycin is an alternate choice. While spiramycin is effective against *Toxoplasma*, it has poor CNS penetration; however, it achieves high concentrations in the placenta and is useful for treatment of toxoplasmosis during pregnancy. Because long-term maintenance therapy is common, particularly in patients with AIDS, a wider choice of antibiotics is urgently necessary, due to potential problems with drug resistance and side effects.

7 Conclusion

Despite major medical advances in the past century, infections of the central nervous system remain a major burden on society. A high index of suspicion, early recognition, and prompt treatment by the clinician remain the best tools to save lives and decrease resultant morbidity from these infections. However, multiple drug-resistant microbes are emerging with the broad-spectrum use of medications, and thus appropriate clinically focused diagnosis and treatment should be the ultimate goal and standard of care.

Key Points

- In patients with bacterial meningitis, delay in treatment is the most critical factor in determining morbidity and mortality; hence, establishing an etiological diagnosis by CSF evaluation in patients suspected of bacterial meningitis is of utmost urgency.
- HSV encephalitis should be treated with intravenous acyclovir; early administration is associated with better prognosis.
- In immunosuppressed patients, CMV infection may cause a ventriculitis with polymorphonuclear leukocytes in the CSF.
- An immunosuppressed HIV-infected patient with focal neurological signs and multiple cerebral ring-enhancing lesions on neuroimaging should be empirically treated for cerebral toxoplasmosis and followed by repeated neuroimaging.
- Steroids may be used in select situations, such as postviral encephalitis, or in conjunction with antimicrobial therapy in bacterial meningitis, tuberculous meningitis, or immune reconstitution syndrome with HIV infection.

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Uncomplicated Skin and Soft Tissue Infections

Ivar L. Frithsen and Cassandra D. Salgado

1 Introduction

Uncomplicated skin and soft tissue infections (SSTI) include the following: impetigo, folliculitis, carbuncles, furuncles, simple abscesses, and cellulitis/erysipelas [1]. This chapter outlines the common bacterial etiologies of these infections as well as reviews current guidelines for their treatment as related to outpatient management. Information regarding the management of bites from animals and from humans will also be presented. Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) will be discussed as an important consideration in the treatment of skin and soft tissue infections. Table 1 outlines the common pathogens causing the various skin infections described in this chapter. Table 2 provides detailed adult and pediatric dosing information for the antibiotics mentioned in this chaptter.

2 CA-MRSA

In several US cities, CA-MRSA is now the most common organism isolated from emergency department patients with skin and soft tissue infections [2]. Approximately 85% of CA-MRSA infections involve the skin or soft tissue, with abscess and folliculitis being the most common presentations [3]. Specific populations have been considered to be at higher risk for developing CA-MRSA skin infections and include the following: athletes, children, military personnel, intravenous drug abusers, prison inmates, and certain ethnic populations [4]. However, many patients with CA-MRSA have no previously identified risk factors and the index of suspicion for the presence of this organism should be based on knowledge of local prevalence rates. Outbreaks of skin infections of any type among patients in settings that involve close personal contact such as families or sports teams should raise suspicion of possible CA-MRSA involvement [5].

I.L. Frithsen (✉)
Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: frithse@musc.edu

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Table 1 Bacterial etiology of skin infections

Diagnosis	Bacterium
Impetigo	
Nonbullous	*Staphylococcus aureus* and *Streptococcus pyogenes* Community-associated methicillin-resistant *Staphylococcus aureus*
Bullous	*Staphylococcus aureus* Community-associated methicillin-resistant *Staphylococcus aureus*
Folliculitis/furuncle/carbuncle	*Staphylococcus aureus* Community-associated methicillin-resistant *Staphylococcus aureus*
Hot tub folliculitis	*Pseudomonas aeruginosa*
Abscess	Polymicrobial *Staphylococcus aureus* Community-associated methicillin-resistant *Staphylococcus aureus*
Cellulitis/erysipelas	*Streptococcus pyogenes* Group B *Streptococci Staphylococcus aureus* Community-associated methicillin-resistant *Staphylococcus aureus*
Bites	Polymicrobial with aerobes/anaerobes *Pasteurella*, *staphylococcal*, and *streptococcal* species *Capnocytophaga canimorsus Eikenella corrodens*

Table 2 Treatment of skin infections[a]

Community-associated methicillin-resistant *Staphylococcus aureus*
First choice: Trimethoprim–sulfamethoxazole (adults) 160/800 mg BID for 10 days
Trimethoprim-sulfamethoxazole (children) 40/200 per 5 ml, 5 ml per 10 kg/dose, (maximum 20 ml) BID for 10 days
Alternatives: Clindamycin[b] (adults) 300–450 mg TID for 10 days
Clindamycin[b] (children) 10–20 mg/kg/day divided into 3 doses for 10 days
Doxycycline (for use in adults only) 100 mg BID for 10 days
Linezolid (adults) 600 mg BID for 10 days
Linezolid (children) 10 mg/kg/dose BID for 10 days

Impetigo
First choice for adults and children: Topical mupirocin 2% TID for 7 days or retapamulin 1% BID for 5 days.
Alternatives: Amoxicillin–clavulanate (adults) 875/125 mg BID for 7 days
Amoxicillin–clavulanate (children) 25 mg/kg/day divided into 2 doses for 7 days
Cephalexin (adults) 250 mg QID or 500 mg BID for 7 days
Cephalexin (children) 25 mg/kg/day divided into 4 doses for 7 days
Penicillin allergic: Clindamycin (adults) 300–450 mg TID for 7 days
Clindamycin (children) 10–20 mg/kg/day divided into 3 doses for 7 days

Table 2 (continued)

Folliculitis/furuncle/carbuncle
First choice: Consider CA-MRSA coverage as noted above and/or
Dicloxacillin (adults) 250 mg QID for 7 days
Dicloxacillin (children) 12.5-25 mg/kg/day divided into 4 doses for 7 days
OR
Cephalexin (adults) 250 mg QID or 500 mg BID for 7days
Cephalexin (children) 25 mg/kg/day divided into 4 doses for 7 days
Hot tub folliculitis
Cefixime (adults) 400 mg daily for 7 days
Cefixime (children) 8 mg/kg/day for 7 days
Ciprofloxacin (for use in adults only) 750 mg BID for 7 days
Abscess
Drainage important, empiric antibiotics for surrounding cellulitis or systemic symptoms
First choice: Consider CA-MRSA coverage as noted above and/or
Amoxicillin–clavulanate (adults) 875/125 mg BID for 7 days
Amoxicillin–clavulanate (children) 25 mg/kg/day divided into 2 doses for 7 days
or
Cephalexin (adults) 250 mg QID or 500 mg BID for 7days
Cephalexin (children) 25 mg/kg/day divided into 4 doses for 7 days
Cellulitis/erysipelas
Consider CA-MRSA coverage if failure of initial treatment
First choices:
Cephalexin (adults) 250 mg QID or 500 mg BID for 7 days
Cephalexin (children) 25 mg/kg/day divided into 4 doses for 7 days
or
Dicloxacillin (adults) 250 mg QID for 7 days
Dicloxacillin (children) 12.5–25 mg/kg/day divided into 4 doses for 7 days
or
Amoxicillin–clavulanate (adults) 875/125 mg BID for 7 days
Amoxicillin–clavulanate (children) 25 mg/kg/day divided into 2 doses for 7 days
Bites
For human bites, consider prophylactic antiretroviral therapy when indicated
First choices:
Amoxicillin–clavulanate (adults) 875/125 mg BID for 7 days
Amoxicillin–clavulanate (children) 25 mg/kg/day divided into 2 doses for 7 days
or
Doxycycline (for use in adults only) 100 mg BID for 7 days

[a]Medication dosages may need to be adjusted for adults with impaired renal function.
[b]Do not use if erythromycin resistant unless negative d-test.

In light of increasing CA-MRSA rates, obtaining standard wound cultures is important for determining appropriate antibiotic coverage. Early recognition and treatment of CA-MRSA infections may help reduce the potential for more severe manifestations of disease such as sepsis or necrotizing pneumonia. Historically, incision and drainage has been considered important in the treatment of skin and soft tissue abscesses. Recent studies have shown this to be an integral step in

management of these infections with drainage considered more important than appropriate antibiotic selection [6]. When choosing an antibiotic for treatment of a known or suspected CA-MRSA infection, it is necessary to understand the mechanism of resistance. Unlike penicillin resistance, which is conferred via production of beta-lactamase, methicillin resistance is conferred through expression of an altered penicillin binding protein [7]. This mechanism of resistance makes the use of combination beta-lactam/beta-lactamase inhibitor antibiotics ineffective. Trimethoprim–sulfamethoxazole (TMP–SMX) and tetracyclines are effective first-line agents in the treatment of CA-MRSA skin infections [3]. Clindamycin may also be considered, but since inducible resistance to *Staphylococcus aureus* can occur, it should be used only when the susceptibility profile is favorable.

3 Impetigo

3.1 Clinical Presentation

Impetigo is a highly contagious skin infection that most commonly affects children, although any age group can be affected [8]. Clinically, impetigo may be divided into two forms: bullous and nonbullous, with nonbullous impetigo accounting for the majority of cases. Body sites most often affected are around the mouth and nose or on the hands and forearms. Nonbullous impetigo begins as a single erythematous macule or papule that rapidly progresses to a vesicle. These vesicles then burst to form characteristic honey colored crusts that can become pruritic [8]; a common affect of scratching is spread to the surrounding areas causes clusters of lesions to form. Bullous impetigo commonly presents as a larger blister containing yellow, serous fluid with clear margins and no surrounding erythema. Yellow crusting and oozing occurs once the bullae rupture [8, 9].

3.2 Epidemiology

Impetigo is the most common pediatric skin infection; it most commonly affects children aged 2–5 [8]. A study in the United Kingdom found that the annual incidence of impetigo was 2.8% for children under 4 years and 1.6% for those aged 5–15 years [10]. Nonbullous impetigo accounts for over 70% of cases. Spread can occur rapidly among close contacts and schoolmates either via direct contact or through contaminated objects such as toys. The highest incidence has been noted to occur in warmer climates or in the summer months and in populations with crowded living conditions and poor hygiene [8].

3.3 Microbiology

Both forms of impetigo are mainly caused by *Staphylococcus aureus* with *Streptococcus pyogenes* contributing to nonbullous forms [8]. If subtypes of

Staphylococcus aureus are those that produce toxins associated with staphylococcal scalded skin syndrome (such as exfolatin), then larger bullae may be noted on clinical exam [11]. CA-MRSA has also been described with impetigo, but the actual incidence of this is unknown.

3.4 Treatment

Impetigo is generally a self-limiting condition that rarely leads to systemic illness or scarring; however, untreated cases can take up to 2 weeks to heal, which can cause significant discomfort for those afflicted and increase the risk of spread to contacts. Since the diagnosis of impetigo is made on the basis of characteristic clinical appearance, wound cultures are not commonly obtained. Therefore, empirical treatment is aimed at the commonly encountered organisms noted above. Of note, post-streptococcal glomerulonephritis occurs in fewer than 1% of cases and treatment of lesions has not been shown to be effective in reducing this complication [10].

A systematic review of the treatment options for impetigo showed that 7 days of topical mupirocin was more effective than placebo [10]. The authors also noted that topical antibiotics may be more effective than some oral antibiotics and that there have been no high-quality studies comparing oral antibiotics to placebo [10]. Despite the limited evidence supporting their use, oral antibiotics are commonly recommended and prescribed for treatment of impetigo. These include amoxicillin plus clavulanic acid, cephalosporins, and macrolides, although increasing rates of erythromycin resistance have been reported. Evidence is also lacking for use of oral antibiotics in cases of severe or extensive impetigo, but, practically speaking, it may be more feasible for some patients to be treated systemically [12]. Clinicians should consider adding coverage for CA-MRSA in the event of a known outbreak or upon initial treatment failure.

4 Folliculitis/Furuncle/Carbuncle

4.1 Clinical Presentation

Folliculitis is an inflammatory reaction to a bacterial infection localized to the hair follicle and affecting the superficial skin layers [13]. Patients may initially develop erythematous, pruritic lesions that can become purulent and can subsequently rupture and drain. Typical lesion locations include the head, back, buttocks, and extremities. Systemic manifestations of folliculitis are rare [14]. Hot tub folliculitis is a distinct entity that results from exposure to contaminated water in hot tubs, whirlpools, or swimming pools. Patients can present with a variety of lesions located on body parts that have been under water, although areas covered by bathing suits are affected more frequently [14]. A similar condition involving nodular lesions of the palms and soles has been reported in children and is referred to as, “hot hand–foot syndrome” [15].

Furuncles are single lesions similar to folliculitis with the exception that they extend into deeper layers of the skin, including the subcutaneous tissue. Lesions are firm, tender, erythematous and can spontaneously drain purulent material. They are commonly found on the face, neck, axilla, and buttocks, as these tend to be moist and hairy areas. Systemic manifestations of furuncles are also rare. Carbuncle is the term used to describe an aggregate of multiple furuncles. Carbuncles are commonly located on the back of the neck, the back, or the thighs. Carbuncles can be painful and commonly involve systemic symptoms such as fever and malaise. Furuncles and carbuncles are sometimes referred to as boils [14].

4.2 Epidemiology

Poor hygiene is a risk factor for developing folliculitis. Hot tub folliculitis generally presents within 48 h of contact with contaminated water and outbreaks have been reported [16]. Furuncles and carbuncles commonly arise from folliculitis. Risk factors for the development of furuncles or carbuncles include obesity, diabetes, chronic kidney disease, impaired neutrophil function, intravenous or subcutaneous drug abuse, and corticosteroid use [14]. These conditions can occur in patients of any age.

4.3 Microbiology

Staphylococcus aureus, including CA-MRSA, is associated with most cases of folliculitis [3]. *Pseudomonas aeruginosa* is the pathogen responsible for the vast majority of cases of hot tub folliculitis. *Staphylococcus aureus* is also the most common causative agent for furuncles and carbuncles [14].

4.4 Treatment

Folliculitis will likely resolve spontaneously in immunocompetent patients without scarring. Warm compresses and topical antibiotics have been used to promote healing and provide symptomatic relief. Proper hygiene should be advocated to avoid recurrent episodes [14]. Small furuncles can be managed in the same manner as folliculitis; however, larger furuncles and carbuncles require incision and drainage. Systemic antibiotic therapy is indicated if the patient is febrile or extensive cellulitis is present surrounding the lesion [5]. Cultures obtained upon incision and drainage can help direct antibiotic therapy when indicated. Empiric antibiotic choices should include agents effective against staphylococci such as semi-synthetic penicillins or first generation cephalosporins. Trimethoprim–sulfamethoxazole is a good choice if CA-MRSA is suspected. Fluoroquinolones and third- and fourth-generation cephalosporins are effective in treating *Pseudomonas* infections and should be used to treat hot tub folliculitis.

5 Abscess

5.1 Clinical Presentation

An abscess is a collection of exudate located within the dermal or deeper layers of the skin. Patients present with single or multiple painful, tender, erythematous nodules that can occur anywhere on the body. These nodules are fluctuant and commonly have an overlying pustule [5].

5.2 Epidemiology

Abscesses can affect individuals of any age. Patients may present with abscesses in various stages of progression. When patients present early, there may be an area of induration with erythema, but no fluctuance is noted. Patients presenting later may have spontaneous rupture of the abscess with development of surrounding cellulitis. Systemic symptoms are rare but are more often noted when there is an area of cellulitis surrounding the abscess [17].

5.3 Microbiology

Abscesses are usually polymicrobial with normal skin flora and other organisms frequently isolated. Guidelines published in 2005 noted that *Staphylococcus aureus* was isolated as a solitary organism from about 25% of drainable abscess [5]. However, a more recent study found that CA-MRSA was isolated from more than 80% of abscesses, thus having profound implications for treatment [2].

5.4 Treatment

Incision and drainage is the mainstay of treatment for abscess. In addition to opening the skin layer, probing is performed to break up loculations. Packing the wound after drainage is commonly performed in order to prevent the incision from closing, which could result in the abscess reforming. However, a pilot study that examined the utility of packing after incision and drainage of an abscess found no reduction in morbidity among patients that did not receive packing. Additionally, the study reported that patients who did get packing experienced more pain and used more pain medication than those whose wounds were not packed [18]. Treatment with antibiotics following incision and drainage remains a topic of debate. For patients with simple abscess and no surrounding cellulitis who have no systemic symptoms, antibiotics are not necessary [17]. If cellulitis or systemic symptoms are present or if the patient is immunocompromised, then antibiotic therapy should be directed toward *Staphylococcus aureus* [17]. Cephalexin can be used, although

a strong suspicion for CA-MRSA should be maintained and empiric treatment with TMP–SMX can be included. Regardless of the decision to use antibiotics, obtaining exudate cultures and close follow-up are important for treatment of abscesses.

6 Cellulitis/Erysipelas

6.1 Clinical Presentation

Cellulitis and erysipelas are terms used to describe similar infections of the skin. Cellulitis is an infection of the skin that involves the deeper dermal layers, including subcutaneous fat. Erysipelas is an infection that affects the upper dermis and superficial lymphatics. Patients who have both of these conditions present with rapidly spreading areas of painful, erythematous warm and edematous skin. Localized lymphadenopathy and dimpling of the skin known as peau d'orange can be present. Vesicles or bullae filled with clear fluid are also commonly noted. Systemic symptoms include fever, tachycardia, hypotension, and leukocytosis; these can be present before skin manifestations are noted. Erysipelas may be distinguished from cellulitis by the presence of a clearly demarcated border of erythema and raised lesions [5].

6.2 Epidemiology

Among 320,000 members of a Utah health plan, Cellulitis accounted for 2.2% of outpatient office visits in 1999 [11]. Extremities are the most common site for cellulitis/erysipelas, although these infections can occur anywhere on the body. It generally occurs where there has been a break in the skin such as an abrasion, although the portal of entry for bacteria is often not identified [17]. Cellulitis and erysipelas can occur in patients of any age, although erysipelas is more common in infants, young children, and older adults. Erysipelas has also been noted to occur more often on the lower extremities [5].

6.3 Microbiology

Cellulitis is still most commonly caused by beta-hemolytic (group A/B) *strep.* Species however, *Staphylococcus aureus*, including CA-MRSA, is becoming more common. Cellulitis can be caused by a wide variety of organisms depending on the circumstances involving development of the infection. Examples include *vibrio* infections following exposure to saltwater and *Haemophilus influenzae,* causing periorbital cellulitis in children [17]. Erysipelas is commonly caused by *S. pyogenes* with rare involvement of group B *Strep* or *Staphylococcus aureus*.

6.4 Treatment

An important first step in the treatment of cellulitis or erysipelas is obtaining a thorough exposure history, as this could provide information that would direct the clinician to consider infection with a less common organism such as *vibrio* mentioned above. Empiric antibiotic therapy generally consists of a first generation cephalosporin such as cephalexin, a penicillinase-resistant penicillin such as dicloxacillin or a beta-lactam/beta-lactamase inhibitor combination such as amoxicillin/clavulanate [3]. One consideration in treating cellulitis is whether or not to obtain blood cultures. A recent review that included five separate studies noted that routine blood cultures for uncomplicated cellulitis were not helpful [19]. However, in the presence of systemic symptoms it is important to consider that a more serious infection may be present and could include hematogenous spread. In these circumstances, further diagnostic studies, including blood cultures, may be beneficial. Close follow-up is important and in the event of treatment failure, coverage to include less common etiologic organisms and CA-MRSA should be considered.

7 Bites

7.1 Clinical Presentation

Each year millions of animal bites occur in the United States with more than 90% of these due to the bites of cats and of dogs [20]. Human bites have been reported as the third most common mammalian bite and present complex management issues [21]. Up to one-half of children will be bitten by a dog during childhood, although the majority of bites are minor and do not require medical attention [22]. Complications from infected bite wounds can result in significant morbidity, including sepsis, meningitis, and endocarditis [23]. Older patients, asplenic patients, those with liver disease, and alcoholics may be more likely to develop serious complications [24]. Patients who seek medical attention less than 8 h after being bitten are less likely to have an established infection as compared to those who present later [20]. Dog bites occur about six times more often than cat bites, but cat bites are more likely to become infected [20, 23].

7.2 Epidemiology

Bites from animals are common, as there are over 160 million dogs and cats in the United States [25]. Dog bites account for up to 80% of animal bites, and this is reflected in the fact that the majority of published data on animal bites pertains to dogs [20]. It was estimated that 4.5 million dog bites occurred in the United States in 1994, which is the most recent year for which published data are available on the overall number of bites [26]. Also in 1994, there were an estimated

333,687 emergency department (ED) visits for dog bites [27], resulting in an estimated 5,991 hospitalizations [28]. A 2001 report estimated that there were 368,245 patients treated in emergency departments with a reported rate similar to previous studies, indicating that rates of dog bites have remained stable. The highest dog bite rates among ED patients occurred in children aged 5–9 and incidence rates declined steadily with increasing age. Dog bites are more likely on the head or face for children and are more common on the arm or hand for adults [29].

Recent data on rates of human bites are not readily available. Human bites can be divided into actual bites or those resulting from a closed fist injury. Bites have been described to occur under a variety of circumstances, for example, during violent encounters such as assaults, among children, and accidentally during sports or sexual activity. Bites also have been reported to occur while attempting to maintain an airway during medical emergencies such as an epileptic seizure. An important consideration in the evaluation of a human bite is the possibility of blood-borne pathogen exposure such as HIV or hepatitis [30].

7.3 Microbiology

Organisms infecting animal or human bite wounds are those from the mouth of the biting animal, normal human skin microbes, and other secondary infectious organisms. Animal and human bite wounds commonly involve both anaerobic and aerobic species. Common pathogens include *Pasteurella* species, *staphylococci,* and *streptococci*. *Capnocytophaga canimorsus* has been reported to cause sepsis and is particularly dangerous for asplenic patients and those with underlying hepatic dysfunction including alcoholics [32]. Human bites have been noted to carry the highest risk of infection with up to 50% infection rates reported from one study [31]. Human bites are typically polymicrobial, but *Eikenella corrodens* is one gram-negative bacillus often recovered along with other organisms. It is not unusual for more than 10 organisms to be cultured from human bite wounds, and one study of 18 human bites in children revealed a total of 97 different bacterial isolates with a range of 1–8 per bite [32].

7.4 Treatment

As with any open wound, the initial treatment should include irrigation, cleansing, and debridement of damaged tissue. Thorough exploration of the wound should be performed to determine if tendon, muscle, or bone damage has occurred. Radiographs should be performed if bone damage is suspected or to detect the presence of a foreign body such as a tooth [32]. Primary closure of bite wounds remains controversial. Empiric antibiotic therapy for animal or human bites is amoxicillin/clavulanate or doxycycline. Due to the large number of potential pathogens isolated from animal and human bite wounds, cultures can be helpful in determining appropriate antibiotic coverage. With animal bites it is important to establish the

rabies status, which will be determined by local health department officials when the bite is reported; in most states this reporting is mandatory. Tetanus immunization status should be assessed and a booster given when indicated. Transmission of human immunodeficiency virus, syphilis, and hepatitis B have been reported following human bite wounds, so it is important to determine the health status of the biter [33]. Prophylactic treatment with antiretroviral agents may be considered for human bites based on a risk analysis [30].

Key Points

- Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is a common cause of skin/soft tissue infections and should be considered regardless of risk factors.
- Empiric antibiotic selection depends on the type of infection and exposure history.
- Wound cultures obtained when initiating empiric therapy will allow detection of resistant organisms and guide subsequent choice of antibiotic in the event of treatment failure.
- Incision and drainage is often essential to allow timely wound healing.

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Septic Arthritis and Osteomyelitis

Camelia E. Marculescu

1 Introduction

Septic arthritis and osteomyelitis are two of the most common diseases that affect bone and joints. Septic arthritis is a true rheumatologic emergency, mandating immediate joint drainage and antibiotics. Adult osteomyelitis most commonly arises from open fractures, diabetic foot infections, or surgical treatment of closed injuries. This chapter provides an overview of the etiology, diagnosis, and antimicrobial management of septic arthritis and adult osteomyelitis.

2 Septic Arthritis

2.1 Overview

The incidenceof septic arthritis in the United States is increasing; the average patient is older, the antimicrobial resistance is rising, and the diagnosis and presentation remains problematic. The incidence of gonococcal arthritis is decreasing, whereas two virulent pathogens methicillin-resistant *Staphylococcus aureus* and group B streptococcus have become more important. Septic arthritis is more often a consequence of occult bacteremia. Breaks in the skin allow staphylococci or streptococci the initial access into the bloodstream. Gram-negative septic arthritis probably arises from bacteremia originating from the urinary or the gastrointestinal tract. Therapeutic joint injections with corticosteroids and rarely arthroscopy can result in iatrogenic septic arthritis [27].

C.E. Marculescu (✉)
Division of Infectious Diseases, Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: marcule@musc.edu

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2.2 Etiology

Most cases of septic arthritis are caused by gram-positive organisms, whereas enteric gram-negative rods account for 43% of the community-acquired bacteremias but cause only 10% of septic arthritis [12, 18].

a. *Staphylococcus aureus is the* most common cause of septic arthritis, which accounts for 44% of cases (Table 1). MRSA may be increasing in importance in septic arthritis. In the last 5 years at Caritas St. Elizabeth's Medical Center and Tufts-New England Medical Center, 25% of septic arthritis was caused by MRSA [27]. In this series, cases were associated with chronic illness, older age, and health-care exposure. Community-acquired MRSA septic arthritis has occurred in some regions of the United States [8].

Table 1 Organisms isolated in 2407 cases of septic arthritis

Organism	No. of isolates (%)
S. aureus	1,066 (44.3)
S. pyogenes	183 (7.6)
S. pneumoniae	156 (6.5)
Haemophilus influenzae	104 (4.3)
Mycobacterium tuberculosis	101 (4.2)
Escherichia coli	91 (3.8)
Coagulase-negative staphylococci	84 (3.5)
N, gonorrhoeae	77 (3.2)
S. agalactiae	69 (2.9)
Pseudomonas aeruginosa	36 (1.5)
N. meningitidis	28 (1.2)
Salmonella sp.	25 (1)
Other gram-negative rods	110 (4.6)
Other β-hemolytic streptococci	104 (4.3)
Polymicrobial	33 (1.4)
Fungi	4 (0.2)
Miscellaneous	136 (5.7)

Adapted with permission from Ross et al. [28].

b. *Hemolytic streptococci* (*Streptococcus agalactiae*) are pathogens encountered especially in the elderly patients, those with diabetes, cirrhosis, and neurologic disease [7], and cause about 10% of septic arthritis [21]. Functional outcomes are typically poor in septic arthritis, due to group B streptococci and other β-hemolytic streptococci [27].
c. *Pneumococcus* causes up to 6% of septic arthritis cases. Pneumococcal septic arthritis is notable for a high frequency of bacteremia and polyarticular disease. Only 50% have an underlying focus of pneumococcal disease such as pneumonia. Mortality in adults is high (19%), although in 95% of survivors, functional outcomes are good [27]. Drug resistance may be an increasing problem [28].

d. *Gonococcal septic arthritis* is a distinct clinical syndrome with a good prognosis. Seventy-five percent of cases occur in women; menses and pregnancy increase the risk of disseminated gonococcal infection [23]. Seventy-two percent of cases are polyarticular and knee involvement is most common. The characteristic hemorrhagic pustules of disseminated gonococcal infection are found in 42% of patients and tenosynovitis in 21%. Urinary signs or symptoms are present in only 32% [27]. Gonococci are recovered from joint fluid in less than 50% of cases. This is probably largely due to the difficulty in recovering these fastidious organisms from cultures but may also indicate that some cases of gonococcal arthritis are immune mediated [23].
e. *Enteric gram-negative rods* cause about 10% of adult septic arthritis especially in populations at risk such as intravenous drug users and elderly patients with comorbid conditions [3, 10]. Recent studies suggest that with prompt diagnosis and therapy, outcomes in older patients may be relatively good [27]. Surprisingly, a urinary source of gram-negative septic arthritis is found only in 50% of elderly patients [20].
f. *Meningococcal septic arthritis.* The incidence of arthritis in invasive meningococcal disease is as high as 14%. The joint fluid may be serous or purulent [27]. Typical presentation is a mono- or oligoarthritis involving large joints, especially the knee. It has been suggested that the arthritis has an immunologic basis, since synovial fluid immune complexes have been detected in several of these patients [9, 30]. The outcome of meningococcal septic arthritis is usually excellent [30].
g. *Coagulase-negative staphylococci.* Typically coagulase-negative staphylococci are considered contaminants when isolated from the joint space in native septic arthritis, but they can be true pathogens after procedures such as arthroscopy and anterior cruciate ligament reconstruction (ACL). It tends to present in an indolent fashion.

Postarthroscopic septic arthritis can be cured with 2 weeks of parenteral antimicrobial therapy, whereas septic arthritis that develops following ACL reconstruction requires arthroscopic debridement and 6 weeks of antimicrobial therapy [1, 14].

2.2.1 Clinical Presentation and Diagnosis

The diagnosis of septic arthritis can be easily established in patients presenting with typical symptoms such as fever, warm, swollen, and exquisitely painful joint. However, high-grade fever is present only in 58% and leukocytosis only in 50–60% of patients [11, 35]. Joint pain can be blunted in immunosuppressed patients. Synovial fluid WBC count is variable. A synovial fluid WBC value of $\geq$50,000 cells/mm^3 is a commonly used threshold for empiric antimicrobial therapy. At least one-third of the patients with native septic arthritis have synovial fluid WBC count < 50,000 cells/mm^3. The yield of synovial fluid culture is increased by inoculation of fluid into blood culture bottles [13]. In cases of undiagnosed arthritis, gram stain and culture of the synovial fluid should be routinely obtained; however, gram staining is insensitive for the diagnosis of septic arthritis [27]. All patients with

suspected septic arthritis should have blood cultures obtained, since bacteremia can be present in at least one-third of the patients with septic arthritis [27]. In gonococcal septic arthritis, less than 50% of synovial fluid cultures are positive, and diagnosis is often based on a compatible clinical syndrome and the isolation of *Neisseria gonorrhoeae* from cultures of the cervix, the urethra, the rectum, or the oropharynx.

2.3 Therapy and Outcome

Septic arthritis is a rapid and destructive disease of the joint space; therefore, broad-spectrum antimicrobial therapy should be initiated before culture data are available. Because synovial fluid tests lack precision for diagnosing septic arthritis, the threshold for starting antibiotics should be low.

- In cases with a negative gram stain of the synovial fluid and if the patient is at low risk for methicillin-resistant *S. aureus* (MRSA) or gonorrhea, cefazolin is a reasonable initial empirical choice for treatment of native septic arthritis.
- In elderly or immunocompromised patients felt to be at risk for gram-negative septic arthritis, empiric antimicrobial therapy should include a broad-spectrum single agent active against streptococci, methicillin-susceptible *S. aureus* (MSSA), and gram-negative bacilli such as cefepime.
- Patients with MRSA risk factors such as hemodialysis, diabetes, recent hospitalization, or nursing home admission should be empirically covered with vancomycin. Community-acquired MRSA infections have been reported in various regions of the Unites States, and it is reasonable to initiate empiric antimicrobial therapy directed against MRSA in patients with septic arthritis in these regions [19]. Limited, but favorable data support the use of linezolid and daptomycin as alternative agents for MRSA septic arthritis.
- Critically ill patients with septic arthritis should receive broad-spectrum antibiotics (e.g., combination therapy with vancomycin and cefepime).
- Sexually active patients that present with clinical syndrome suggestive of gonococcal infection should receive ceftriaxone. Septic arthritis that occurs as a result of human or animal bites should receive agents active against oral flora such as ampicillin–sulbactam.
- Intravenous drug users with septic arthritis may be empirically covered with vancomycin and an antipseudomonal agent.

Recommendations for empiric antimicrobial therapy are summarized in Table 2. Once the causative organism has been identified, the antimicrobial therapy should be narrowed.

Duration of therapy: In general, it is recommended to complete at least 3 weeks of antimicrobial therapy, which may include a period of step-down oral therapy. Gonococcal septic arthritis can be treated with 2 weeks of ceftriaxone.

Table 2 Empiric antibiotic therapy of suspected septic arthritis

Gram stain of synovial fluid	Antibiotic therapy
Gram-positive cocci	
No risk factors for MRSA (see text)	Cefazolin, 2 g IV q 8 h
MRSA risk factors or β-lactam allergy	Vancomycin, 1 g IV q 12 h
Gram-negative cocci (presumptive *Neisseria* sp.)	Ceftriaxone, 1 g IV q 24 h
Gram-negative rods	Cefepime, 2 g IV q 8 h or piperacillin–tazobactam, 4.5 g IV q 6 h
No organisms on gram stain	
Previously healthy, low MRSA risk	Cefazolin, 2 g IV q 8 h
MRSA risks present	Vancomycin, 1 g IV q 12 h plus cefepime, 2 g IV q 8 h or piperacillin–tazobactam, 4.5 g IV q 6 h

Abbreviation: MRSA, methicillin-resistant *S. aureus*.
Adapted with permission. Ross, Septic arthritis [27].

Courses of 4–6 weeks are recommended for patients with septic arthritis that involve sternoclavicular and sacroiliac joints [27, 29].

Joint drainage decompresses the joint, improves blood flow, and removes bacteria, toxins, and proteases. Arthrocentesis should be repeated daily until effusions resolve and cultures are negative. Surgical drainage is recommended for native hip septic arthritis, for failure to respond after 5–7 days of arthrocentesis and antibiotics, for pus in the joint space, and for soft tissue extension of infection [27]. The shoulder joint should be drained surgically or under radiologic guidance [26, 32]. No good data show a superiority of surgical drainage versus arthrocentesis. Aggressive rehabilitation is needed to prevent joint contractures and muscle atrophy, and mobilization should be done as soon as pain allows [27].

3 Adult Osteomyelitis

3.1 Overview

Osteomyelitis is a disease very heterogeneous in its pathophysiology, in its clinical presentation, and in its management. It is felt to be one of the most difficult infectious diseases to treat. The hallmarks of osteomyelitis are the formation of the sequestra and progressive bone destruction. Osteomyelitis can result from hematogenous seeding, from contiguous spread of infection, or from direct inoculation of the microorganisms into the bone. There are several classifications of osteomyelitis: the two major classifications are those by Waldwogel [34] and Cierny–Mader [6]. The Waldvogel classification takes into account the duration of disease (acute or chronic), the mechanism of infection (hematogenous or contiguous), and the presence of vascular insufficiency. The Cierny–Mader classification

Table 3 Cierny–Mader staging system

Anatomic type	Physiologic class
Stage 1: Medullary osteomyelitis	A Host: Normal host
Stage 2: Superficial osteomyelitis	B Host: Systemic compromise (Bs)
Stage 3: Localized osteomyelitis	Local compromise (Bl)
Stage 4: Diffuse osteomyelitis	Systemic and local compromise (Bls)
	C Host: Treatment worse than the disease
Systemic or local factors that affect immune surveillance, metabolism, and local vascularity	
Systemic (Bs)	*Local (Bl)*
Malnutrition	Chronic lymphedema
Renal, hepatic failure	Venous stasis
Diabetes mellitus	Major vessel compromise
Chronic hypoxia	Arteritis
Immune disease	Extensive scarring
Malignancy	Radiation fibrosis
Extremes of age	Small vessel disease
Immunosuppression or neuropathy	Complete loss of sensation
Immune deficiency	Tobacco abuse

Adapted after Calhoun and Manring [5], with permission.

is determined by the status of disease process, and it is based on the portion of the bone affected, the physiologic status of the host, and other risk factors (see Table 3).

3.2 Etiology

The specific microorganism isolated from patients with bacterial osteomyelitis is often associated with the age of the host or a common clinical scenario (see Table 4). Hematogenous osteomyelitis is almost always a monomicrobial infection, with *S. aureus* being the most prevalent causative organism [31]. Coagulase-negative staphylococci, aerobic gram-negative bacteria, and *Peptostreptococcus* spp. are also frequently isolated in long bone osteomyelitis [31]. Posttraumatic osteomyelitis resulting from open fractures is often polymicrobial. Staphylococci and gram-negative aerobic and anaerobic bacilli are most frequently isolated. Other microorganisms such as enterococci, fungi, and atypical mycobacteria have been implicated in the etiology of osteomyelitis as well. *Staphylococcus aureus* and coagulase-negative staphylococci are the most common microorganisms encountered in vertebral osteomyelitis. Vertebral osteomyelitis caused by gram-negative aerobic bacilli and *Candida* spp. are more commonly seen in intravenous drug users, immunosuppressed patients, and in the postoperative setting [31]. Contiguous-focus osteomyelitis associated with diabetes mellitus or vascular insufficiency is often polymicrobial (*S. aureus*, β-hemolytic streptococci, enterococci, anaerobes).

Table 4 Microorganisms isolated from patients with bacterial osteomyelitis

Microorganism	Most common clinical association
S. aureus (susceptible or resistant to methicillin)	Most frequent microorganism in any type of osteomyelitis
Coagulase-negative staphylococci or *Propionibacterium*	Foreign body-associated infection
Enterobacteriaceae or *P. aeruginosa*	Common in nosocomial infections
Streptococci or anaerobic bacteria	Associated with bites, fist injury caused by contact with another person's mouth, diabetic foot lesions, and decubitus ulcers
Salmonella or *S. pneumoniae*	Sickle cell disease
Bartonella henselae	Human immunodeficiency virus infection
Pasteurella multocida or *Eikenella corrodens*	Human or animal bites
Aspergillus, *Mycobacterium avium* complex, or *Candida albicans*	Immunocompromised patients
M. tuberculosis	Populations in which tuberculosis is prevalent
Brucella, *Coxiella burnetii* (chronic Q fever), or other fungi found in specific geographic areas	Populations in which these pathogens are endemic

Adapted with permission from Lew and Waldwogel [16].

3.3 Diagnosis

The typical presentation of acute osteomyelitis is with acute pain and febrile episode. Presence of chronic drainage, sinus tract or pain, relapses in the same affected area, and exposed bone are symptoms that suggest chronic osteomyelitis. In general, persistence of clinical symptoms for more than 10 days is suggestive of chronic osteomyelitis. However, the hallmark of chronic osteomyelitis is the presence of necrosis on bone histology rather than duration of symptoms. Chronic osteomyelitis is a long-standing infection that lasts over months or years. It implies persistence of microorganisms, low-grade inflammation, sequestrum, and fistulous tract formation. Laboratory data are primarily useful as a benchmark against which treatment response is measured. Leukocyte count is not a reliable indicator of infection, since its sensitivity is only 26% [4]. Sedimentation rate has a sensitivity between 50 and 90%; it could be normal early in the course of disease, and it decreases slowly over months in response to therapy. C-reactive protein (CRP) has a sensitivity of 71% and is more reliable than sedimentation rate for follow-up. CRP increases within hours from infection and returns to normal within 1 week after effective therapy [4], with the caveat that in rheumatologic or inflammatory conditions, these markers are less reliable and more difficult to interpret.

Imaging studies are helpful when diagnosis of osteomyelitis is equivocal or when there is a need for the determination of the extent of soft tissue/bone abnormalities in preparation for surgical intervention [18]. In hematogenous osteomyelitis,

radiographic changes usually reflect the destructive process but lag at least 2 weeks behind the evolution of infection. The earliest changes are swelling of the soft tissue, periosteal thickening, and/or elevation, and focal osteopenia [18]. A recent meta-analysis of 23 studies in chronic osteomyelitis showed that leukocyte scintigraphy has 84% accuracy in the peripheral skeleton and PET-FDG is superior for the axial skeleton [33]. Indications and limitations of selected imaging studies are presented in Table 5.

The diagnosis and the determination of the cause of osteomyelitis rest on the isolation of the pathogen(s) from the bone lesion or from the blood or the joint culture. Superficial cultures obtained from the drainage site are usually contaminated with skin flora. The use of antibiotics prior to surgical culture ascertainment reduces the sensitivity of the culture; therefore, whenever possible, cultures of the bone should be obtained prior to initiation of antimicrobial therapy. Cultures of the bone biopsy yield a microbiologic diagnosis in 94% of cases [36]. In general, antimicrobial therapy should be stopped for 10–14 days prior to any diagnostic procedure, unless soft tissue infection is present, unless microbiology is already known, unless patient is septic, or unless the risk of secondary bacteremia and hematogenous infection is high. Sinus tract cultures are not reliable in predicting the microorganism isolated from the infected bone [17]. However, sinus tract cultures that grow *S. aureus* show a positive correlation with bone cultures [18].

The gold standard in diagnosing chronic osteomyelitis is bone biopsy obtained before or at the time of surgical debridement. Cultures of the bone yield a microbiologic diagnosis in 94% of cases [17]. At least three intraoperative tissue samples for aerobes and anaerobes should be obtained routinely to facilitate the distinction between an intraoperative contaminant and a true pathogen [2, 4].

3.4 Treatment

Appropriate therapy of osteomyelitis includes the following: adequate drainage, thorough debridement, obliteration of dead space, wound protection, and specific antimicrobial coverage. If the patient is a compromised host, then efforts should be made to correct or improve the host defects (e.g., good nutrition, diabetes control, smoking cessation programs).

a. Surgical management of osteomyelitis can be very challenging. The goal of debridement is to leave healthy, viable tissue until punctuate bleeding is noted ("paprika" sign) [18]. Adequate debridement may leave a large bone defect termed "dead space." The adequate management of dead space may include local tissue flaps or free flaps, cancellous bone grafting, antibiotics-impregnated acrylic beads, or antibiotic-impregnated biodegradable beads [18]. Stabilization of the bone is needed when movement at the site of infection is present and can be achieved by using screws, rods, and/or an external fixator. Adequate soft tissue coverage of the bone is necessary to arrest osteomyelitis and can be achieved with the use of split thickness grafts for small defects or free muscle flaps and free vascularized muscle flaps for larger defects [18, 24].

Table 5 Indications and limitations of selected imaging studies in chronic osteomyelitis

Imaging modality	Advantages/indications	Limitations
Tri-phase bone scan	– High sensitivity (~70%); can differentiate cellulitis from osteomyelitis, specificity 25%; negative bone scan excludes osteomyelitis	– Trauma, hardware, surgery, neuropathy, diabetes mellitus can cause a false-positive bone scan – Specificity 38–79% – Can be positive for 1–2 years after treatment
Gallium scan	– More specific than bone scan (67%) – Returns to normal after successful therapy – Can be combined with Tc scan	– False positive from fractures, tumor – Image takes longer
WBC scan (In or Tc)	– Increased specificity compared to bone scan in complicating conditions – Good accuracy in peripheral skeleton	– Loss of sensitivity for axial skeleton – Does not delineate anatomy in the extremities, especially when circulatory compromise is present
CT	– Exceptional bony detail; best for detection of sequestrum, small foci of gas in the medullary canal – Important in presurgical evaluation of the extent	– Metallic implants-artifacts
MRI	– Highly sensitive (greater than CT) for detecting osteomyelitis as early as 3–5 days – Differentiates between soft tissue and bone infection – Determines the extent of infection – Helps planning the optimal surgical management – Defines critical adjacent structures – Differentiates osteomyelitis from neoplasm or neuropathic joint in diabetic foot, avascular necrosis from osteomyelitis, infections in patients with rheumatoid arthritis	– Not useful in whole-body examinations – Metal implants-artifacts
PET-FDG	– High accuracy, especially in the axial skeleton – Allows differentiation between osteomyelitis and soft tissue infections	– Early bone healing can be confused with osteomyelitis – Avoid in the first 3–6 months in postsurgical/posttraumatic bone healing – Limited usefulness in prosthetic joint infections or tumor

Data from Pineda et al. [25].

b. Antimicrobial management: Following culture ascertainment, a parenteral antimicrobial regimen is begun to cover the clinical suspected pathogens. Once the organism is identified, a specific antibiotic class(es) can be selected by appropriate sensitivity method (see Table 6). The optimal duration of therapy in osteomyelitis is

unknown. Many experts advocate a total duration of 4–6 weeks of parenteral therapy from the last major debridement surgery. The duration of therapy is primarily based on experimental studies that showed that 4 weeks of therapy was more effective in sterilizing the bone than was 2 weeks [22]. Furthermore, it takes up to 6 weeks for the debrided bone to be covered with vascularized soft tissue. Outpatient intravenous antimicrobial therapy is typically given via a long-term intravenous catheter such

Table 6 Suggested antimicrobial therapy for selected microorganisms in adults with chronic osteomyelitis

Microorganism	First choice[a]	Alternative[a]
Staphylococcus spp., oxacillin susceptible	Nafcillin sodium, 1.5–2 g IV q 4 h or Cefazolin, 1–2 g IV q 8 h	Vancomycin, 15 mg/kg IV q 12 h or Levofloxacin, 500–750 mg PO or IV q 24 h + rifampin, 300–450 mg PO q 12 h[b]
Staphylococcus spp., oxacillin resistant	Vancomycin, 15 mg/kg IV q 12 h	Linezolid, 600 mg PO or IV q 12 h or Levofloxacin, 500–750 mg PO or IV q 24 h+ rifampin, 300–450 mg PO q 12 h[b]
Enterococcus spp., penicillin susceptible[c]	Aqueous crystalline penicillin G, 24–30 million units IV q 24 h continuously or in six divided doses or Ampicillin sodium, 12 g IV q 24 h continuously or in six divided doses	Vancomycin, 15 mg/kg IV q 12 h
Enterococcus spp., penicillin resistant[c]	Vancomycin, 15 mg/kg IV q 12 h	Linezolid, 600 mg PO or IV q 12 h
P. aeruginosa [d]	Cefepime, 1–2 g IV q 12 h or Meropenem, 1 g IV q 8 h or Imipenem, 500 mg IV q 6–8 h	Ciprofloxacin, 750 mg PO or 400 mg IV q 12 h or Ceftazidime, 2 g IV q 8 h
Enterobacter spp.	Meropenem, 1 g IV q 8 h or Imipenem, 500 mg IV q 6–8 h	Cefepime, 1–2 g IV q 12 h or Ciprofloxacin, 750 mg PO or 400 mg IV q 12 h
β-Hemolytic streptococci	Aqueous crystalline penicillin G, 20–24 million units IV q 24 h by continuous infusion or in six divided doses or Ceftriaxone, 1–2 g IV q 24 h Aqueous crystalline penicillin G, 20–24 million units IV q 24 h by continuous infusion or in six divided doses	Vancomycin, 15 mg/kg IV q 12 h Clindamycin, 600–900 mg IV q 8 h

Table 6 (continued)

	or Ceftriaxone 1–2 g IV q 24 h or
Propionibacterium acnes and *Corynebacterium* spp.	Vancomycin, 15 mg/kg IV q 12 h

[a]Dose adjustment necessary for renal impairment.
[b]Levofloxacin–rifampin combination therapy for patients managed by debridement with retention.
[c]Addition of aminoglycoside for bactericidal synergy is optional. Considerations in choice of an agent are similar to those noted for treatment of enterococcal endocarditis.
[d]Addition of an aminoglycoside is optional.
Adapted with permission from Sia et al. Prosthetic joint infections, Infect Clin North Am. 2005:19; 885–914.

as peripherally inserted central catheter (PICC line) [31]. Oral therapy using drugs with excellent bioavailability such as fluoroquinolones, clindamycin, trimethoprim–sulfamethoxazole, metronidazole, fluconazole, and linezolid may be considered in select patients [15].

Key Points

- The incidence of septic arthritis in the United States is increasing, *S. aureus* being the main pathogen causing septic arthritis.
- Septic arthritis is a true rheumatologic emergency, mandating immediate joint drainage and antibiotics.
- Osteomyelitis can result in severe morbidity. Bone biopsy is the gold standard of diagnosis.
- Microbiologic diagnosis is crucial for appropriate antimicrobial therapy. Bone cultures should be obtained in the absence of antimicrobial therapy whenever possible.
- Surgical management is crucial in the management of chronic osteomyelitis. It is typically followed by directed, long-term intravenous antimicrobial therapy, which is often administered on an outpatient basis.

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Human Immunodeficiency Virus (HIV): Acquired Immune Deficiency Syndrome (AIDS)

Frank Romanelli

1 Introduction

Within the United States, the first clinical cases of HIV infection were reported as early as 1981 [1]. These initial cases involved previously healthy gay, white males who presented to clinicians with various opportunistic infections including *Pneumocystis jiroveci* pneumonia (PCP) [1]. With little epidemiologic data available, homosexuality appeared to be the most significant risk factor for this "new" disease and the term gay-related immune deficiency (GRID) became popular. After more data revealed that sexual preference was not a true risk factor and that a virus was the causative organism, GRID would later be re-termed HIV.

Following the report of these initial cases, HIV infection rates across the United States increased. Lack of knowledge regarding the exact mechanisms by which the disease was transmitted contributed to behaviors and policies that failed to stem this expansion in disease incidence and prevalence. In the mid-1980s, the virus was isolated and a screening test became available. Because no therapies were yet defined, acquisition of HIV infection at this time predictably resulted in the development of AIDS; life expectancies following an AIDS diagnosis typically ranged from 2 to 4 years.

As researchers garnered more information regarding the pathophysiology associated with HIV infection, various therapies became available. The era of antiretroviral therapy was heralded in 1987 by the introduction of the nucleoside reverse transcriptase inhibitor zidovudine [2]. Soon after its introduction it became clear that the use of zidovudine alone would not be sufficient to control or eradicate HIV infection. The Centers for Disease Control (CDC) reported that prior to the advent of combination therapy involving protease inhibitors, AIDS was the number one cause of death among American males aged 25–44 [3]. Subsequently, several additional antiretroviral drugs were developed and multi-drug therapy became the

F. Romanelli (✉)
Clinical Specialist in HIV/AIDS, College of Pharmacy, University of Kentucky, Lexington, KY, USA
e-mail: froma2@uky.edu

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standard of care. Combination therapy has significantly impacted the life expectancies of patients living with HIV but is not a cure for the disease. Despite the lack of curative approaches, the efficacy of current drug therapies has changed HIV management to require an emphasis on chronic care. While highly beneficial, the use of combination antiretroviral therapy is still associated with significant limitations, including adverse side effects, compromises in quality of life, and a high economic burden.

2 Clinical Course

The clinical course of HIV varies from individual to individual. Infection initially results in an acute phase that is characterized by high levels of viral replication and dissemination [4]. Typically the acute phase manifests as constitutional symptoms including rash, fever, weight loss, fatigue, night sweats, and adenopathy; patients frequently attribute these non-specific symptoms to other causes. These symptoms may occur within days to weeks of initial infection and typically last approximately 14 days [4]. Because HIV antibodies may take weeks to achieve detectable levels, routine antibody testing to establish a diagnosis during this early time may produce "false negatives," a phenomenon called the "window period" [4].

Following the acute phase, an asymptomatic period usually follows and is characterized by a reduction in viral burden [4]. The reduction in viral load is thought to be due to immune responses that are partially effective in limiting viral replication. Following this initial drop in viral load, a set point of viral activity is usually achieved. Individuals experiencing higher viral load set points have a faster progression to AIDS. Eventually viral replication begins to exceed the immune response with resultant declines in $CD4^+$ cell counts and increases in viral load. The decline in functional $CD4^+$ cells is associated with increased susceptibility to numerous opportunistic infections which may or may not be life-threatening [4].

3 Epidemiology

HIV infection rates are usually reported as sub-divided into either an "HIV" or an "AIDS" category [4]. Persons are termed as being "HIV positive (HIV+)" after two consecutive HIV enzyme-linked immunosorbent assay (ELISA) tests are positive, and these findings have been confirmed via a Western blot. An HIV+ patient is said to have AIDS if the $CD4^+$ cell count is or ever has been less than 200 cells/mm [3] or if the patient develops one of the many opportunistic infections termed as "AIDS-defining illnesses" [5]. These AIDS-defining illnesses include, among others, tuberculosis, toxoplasmosis, *Pneumocystis jiroveci* pneumonia (PCP), and Kaposi's sarcoma (Table 1) [6].

Worldwide, approximately 40 million people are infected with HIV; of those, approximately 18 million are female [7]. Globally, in 2006 alone, an estimated 2.6 million individuals died from AIDS [7]. The majority of infections worldwide are

Table 1 Common AIDS-defining illnesses

- *Pneumocystis jiroveci* pneumonia
- Wasting syndrome
- Kaposi's sarcoma
- Esophageal or pulmonary candidiasis
- *Mycobacterium avium–intracellulare* complex
- Cytomegalovirus retinitis and other CMV diseases
- HIV encephalopathy
- Extra-pulmonary cryptococcosis
- Toxoplasmosis
- Lymphoma
- Cryptosporidiosis
- Tuberculosis
- Histoplasmosis
- Progressive multifocal leukoencephalopathy
- Coccidioidomycosis
- *Salmonella* septicemia

transmitted by heterosexual contact (75%), and the disease continues to be a major public health issue and crisis in most underdeveloped and unindustrialized nations [7]. The visible effects of HIV and AIDS are probably most evident in the continent of Africa, where, in many countries, HIV disease alone has decreased average life spans by decades. Limited access to medications and prevention education continues to contribute to the HIV dilemma in resource-poor areas. In regard to pediatric infections, vertical transmission is responsible for more than 90–95% of all childhood cases of HIV [1, 3, 7].

In the United States, approximately 1,000,000 individuals are believed to be living with either HIV and/or AIDS as reported through 2005 [8].

Approximately 31% of these individuals are women. Unlike global estimates, AIDS rates in the United States have steadily declined. Patients with HIV infection are living longer. In 1996a 17% decrease in deaths from AIDS was reported. Unfortunately, HIV infection rates remain unchanged. In some subsets of populations, such as younger gay men and heterosexual women, a trend toward increased infection rates has been noted. In the United States, a disproportionate burden of HIV infection occurs among minorities (especially African-Americans and Hispanics). Increases are also observed among people living in poor, rural areas. The majority of American HIV-infected individuals continue to reside in urban areas, with Washington, DC, having the highest infection rate per person. Men who have sex with men (MSM) compromise the largest exposure category in the United States (35%), followed by those with high-risk heterosexual contact (20%) and injection drug users (14%) [8].

4 Transmission

Compared to most viral particles, HIV is difficult to transmit. The virus requires significant exposure in order for transmission to occur. HIV has not been shown to be transmitted by casual contact and it appears to be unstable when exposed to the

environment [9]. Transmission almost always involves exposure to blood, semen, or vaginal fluids from HIV-seropositive individuals.

Exchange of bodily fluids most often occurs through sexual contact [9]. Anal intercourse, likely because of its traumatic nature, carries the highest risk of disease transmission. In terms of risk, vaginal intercourse and receptive oral sex with ejaculation follow anal intercourse. A great deal of speculation has surrounded the true risk associated with oral sex. Epidemiologic trials in this area are limited by the extent of truthfulness regarding sexual practices that are reported by study participants. When used appropriately, barrier methods including latex condoms and dental dams have been shown to reduce the rate of disease transmission. In patients with latex allergies, the use of more costly polyurethane-based condoms and/or dental dams should be advised [10]. It should be noted that while effective at reducing risk, neither dental dams nor latex condoms will entirely eliminate risk. Abstinence is the only practice which will entirely preclude the risk of HIV transmission from sexual contact.

Intrauterine transmission of HIV remains the leading cause of pediatric infections in the United States [9, 11]. The use of zidovudine (AZT) has been shown to effectively reduce the potential risk of perinatal transmission by approximately 68% [12, 13]. For HIV-infected pregnant women, zidovudine should be administered at doses of 100 mg PO five times per day beginning at 14–34 weeks of gestation, followed by an intravenous zidovudine 2 mg/kg load and, during delivery, a 1 mg/kg/h infusion. The neonate should then be administered at 2 mg/kg of zidovudine PO q6h for the first six weeks of life [11]. Some researchers have explored the utility of simpler, shorter antiretroviral regimens involving the non-nucleoside reverse transcriptase inhibitor nevirapine.

Due to their propensity to induce resistance in infected women, these short-course antiretroviral therapies to prevent maternal–child transmissions have raised concerns. Pregnancy is not considered a reason to defer appropriate antiretroviral therapy. In caring for HIV-positive women who become pregnant and wish to continue antiretroviral therapy, it may be advisable to include AZT as part of any three-drug regimen because of its proven efficacy in protecting the fetus. Even the sole use of AZT during pregnancy, labor, or by the newborn infant may reduce transmission; treatment should be offered at whatever stage the women enters the health-care system. Current CDC recommendations emphasize the importance of HIV testing as part of the routine care of pregnant females and an “opt-out” strategy is recommended.

Injection drug users (IDUs) are at risk for HIV transmission from the exchange of potentially contaminated needles and syringes. While rehabilitation treatment remains paramount, IDUs should be intensively counseled regarding the importance of using clean needles and associated paraphernalia (e.g., “works”) whenever possible. If sterile needles/syringes are not available, disinfection of needles/syringes with at least two washings of a minimum of 30 s in duration using undiluted household bleach (i.e., Clorox®) may be advised [13]. Some states and other jurisdictions have enacted pharmacy syringe sales and/or syringe exchange programs as public health responses to the epidemic.

Standard OSHA precautions have lowered the incidence of exposures within occupational settings. Standard precautions dictate that all bodily fluids should be considered infectious regardless of the source patient; thus appropriate precautions and barriers should always be employed (e.g., face masks, gloves, gowns, and eye guards). Needles should never be re-capped or broken by health-care professionals. Used needles and other sharps such as scalpels should be disposed of in proper needle receptacles as per OSHA standards [17]. The risk of contracting HIV from a needlestick is approximately 0.32% [14, 16]. The risk of seroconversion is likely correlated with the source patient's viral load.

The use of post-exposure prophylaxis (PEP) has been demonstrated to reduce the risk of occupational transmission by upwards of 79% [14]. When an exposure has occurred, the extent of contact with potentially infectious materials (i.e., blood, mucous) should guide the selection of the PEP regimen to be used. In cases involving less severe exposures (i.e., mucous membrane), a dual nucleoside reverse transcriptase inhibitor-based regimen may be appropriate (i.e., zidovudine plus lamivudine, or lamivudine plus stavudine, or tenofovir plus emtricitabine) [15]. In more serious exposures (i.e., needlesticks), a three-drug regimen, which includes two nucleoside reverse transcriptase inhibitors and a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor, should be used (i.e., any two basic regimen selections plus lopinavir/ritonavir or efavirenz). Specific drug selections may vary depending upon individual factors including the patient's past medical history and the antiretroviral history of the source patient (if available). Drug therapy should be initiated as soon as possible (ideally within 2 h of exposure) and be continued for a minimum of 30 days. Exposed individuals should be offered HIV ELISA testing at baseline, 6 weeks, 12 weeks, and 6 months post-exposure. The use of PEP following non-occupational exposures (i.e., sexual) is controversial and should be considered within 72 h of exposure and on a case-by-case basis [18].

5 Diagnosis

As previously mentioned, the HIV ELISA test is the accepted screening assay for HIV. This test detects the presence of HIV antibodies within the serum. While highly sensitive, the ELISA is also relatively non-specific; thus, it is important to test further to rule out a false-positive test result. In cases where a patient's HIV ELISA is reactive, the test should be repeated and then confirmed with a Western blot assay. In an attempt to improve screening processes, some rapid and alternative testing systems have been developed. OraQuick Advance® is an ELISA system approved for use with oral fluids or fingerstick blood specimens with a 20 min turnaround time. Additionally, OraQuick Advance® is CLIA waived by the FDA, thus allowing various health-care professionals to perform the test outside of the auspices of a clinical laboratory [19].

In the earlier years of the epidemic, HIV testing was advised for high-risk groups (e.g., MSM, IDU) and limited by stringent consenting rules. Recently, the CDC amended its earlier recommendations regarding the screening and diagnosis of HIV

and now advocates that all persons aged 13–64 years of age be screened as a part of routine health examinations [20]. Additionally, HIV screening is now considered a test of dissent rather than consent. The impetus for wider screening practices is based on data which indicate that as many as one-third of all HIV-infected patients in the United States are unaware of their status. By expanding screening protocols, the CDC hopes to capture more of these unknown diagnoses as well as de-stigmatize the entire HIV testing procedure. Regardless of the initial screening test employed, patients should be informed of their HIV status only after confirmation with a Western blot assay. Since antibody production following infection with HIV may not occur for 3–6 months, a negative ELISA test does not negate the possibility of infection [20]. Patients testing negative should be advised to consider repeat testing 6 months later.

6 Pathogenesis

HIV exists in two distinct forms, HIV-1 and HIV-2. HIV-1 is known to be more virulent than is HIV-2 [21]. HIV-1 compromises approximately 99% of all cases in the United States. In contrast, HIV-2 is more prevalent in Africa. Unlike other viral entities, HIV has a remarkable capacity both to replicate and to mutate. The virus produces up to 10^{10} new particles per day, while committing 10^4 errors per base pair incorporated into its genome [21]. This high rate of production coupled with an error-prone replication cycle translates into a high propensity for the rapid emergence of drug resistance.

Once HIV enters the bloodstream it seeks out and infects $CD4^+$ cells [4, 21]. $CD4^+$ cells, named for their $CD4^+$ receptors, play critical roles in the recruitment, maintenance, and control of immune system functions (Fig. 1). HIV infects $CD4^+$ cells through mechanisms involving interactions with the $CD4^+$ receptor as well as with one of two co-receptors (CCR5 or CXCR4) [22, 23]. Viral strains, which are preferentially trophic for the CXCR4 co-receptor, have been associated with greater virulence and patients infected with these strains have an increased likelihood of progression to AIDS. HIV carries out its replication cycle within infected $CD4^+$ cells. As a retrovirus, HIV's baseline genetic material is RNA. Using the enzyme reverse transcriptase, HIV will transcribe its viral RNA into viral DNA. This viral DNA is then integrated into host cell human DNA via an enzyme known as integrase. Once viral DNA is incorporated into the host $CD4^+$ cell, it will be inadvertently translated into viral proteins. Viral proteins are large polypeptides which must be cleaved for activation by "scissor-like" enzymes known as proteases. Once these polypeptides have been cleaved and activated, the virus leaves the host $CD4^+$ cell to infect another cell. The processes involved in the departure of the newly formed viral particles result in the death of the host cell. Thus viral load increases, while $CD4^+$ cell counts decrease. As the $CD4^+$ cell counts decrease, the infected person becomes increasingly susceptible to various opportunistic infections (OIs) including tuberculosis, Kaposi's sarcoma, toxoplasmosis, candidiasis, and various other diseases (Table 1) [6] as well as increased rates of some cancers. The infected patient

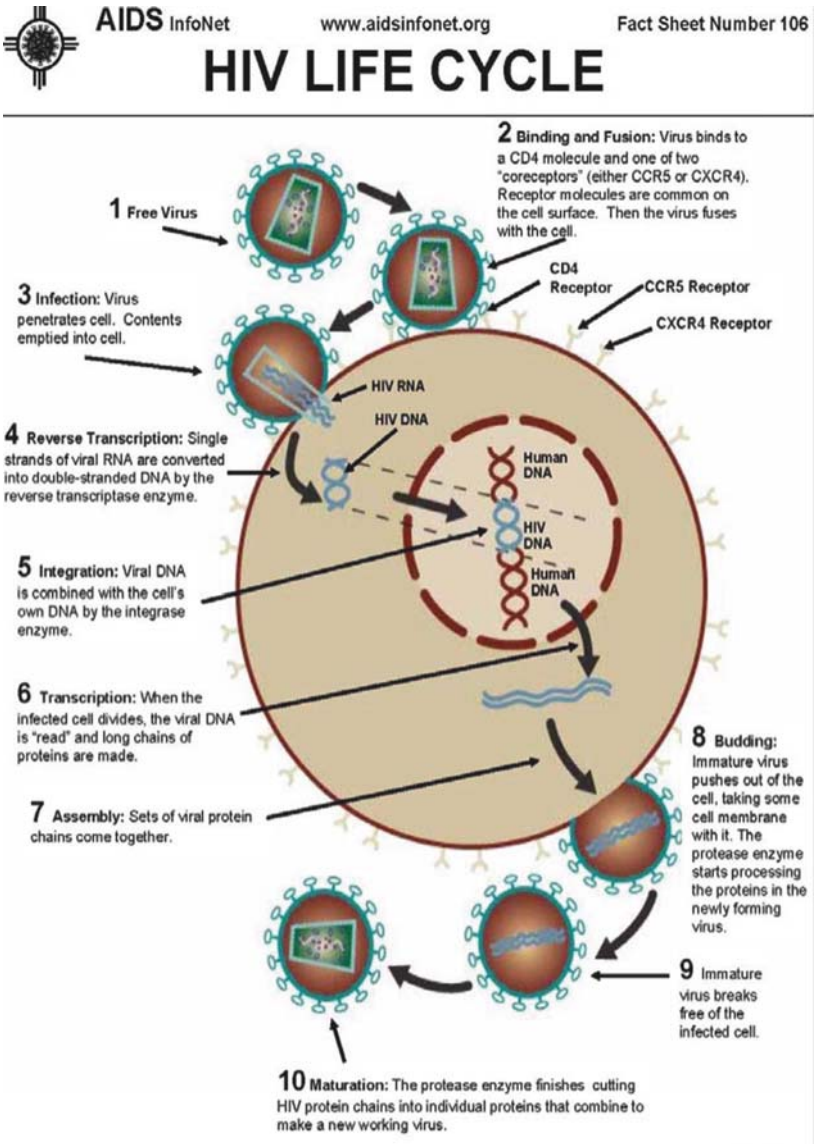

Fig. 1 HIV replication cycle

usually dies not as a result of HIV disease itself but rather from secondary infections or malignancies that occur as a result of ongoing immune destruction. As effective therapies have become more available in the United States, it is now recognized that many patients with HIV infection will die from other non-HIV-related causes. This highlights the role of primary care in the treatment of HIV-infected patients.

These individuals will require attention to standard health-related issues including diet and exercise, cancer screening, counseling regarding healthy lifestyles, management of chronic diseases, and attention to prevention and wellness issues that maximize overall health.

The incidences of many OIs seen in patients infected with HIV have been correlated with specific $CD4^+$ cell count breakpoints. Therefore, prophylactic regimens against various OIs are initiated at specific cell counts in the hopes of circumventing disease acquisition [6]. For example, when the $CD4^+$ cell count of an individual patient falls below 200 cells/mm^3, a prophylactic regimen of Bactrim DS® 1 PO QD should be prescribed to prevent *PCP*. When the $CD4^+$ cell count falls below 50 cells/mm^3, a regimen of azithromycin 1,200 mg weekly should be prescribed for prophylaxis against *Mycobacterium avium* complex (MAC). The addition of these prophylactic regimens often complicates medication regimens for patients infected with HIV and contributes to the overall incidence of drug-related adverse effects. In cases where $CD4^+$ cell counts rise above prophylactic breakpoints for a specified period of time and in the presence of a sufficiently controlled viral load, it may be appropriate to discontinue these drugs [6].

7 Pharmacotherapeutics

Primary care providers and extenders play distinct roles in the screening and referral process involved in HIV infection. As the life expectancies of patients infected with HIV continue to increase, primary care providers will likely encounter greater numbers of HIV-infected patients within their practices. These patients will face many of the same health-related issues that non-HIV-infected patients encounter. Additionally, these patients may suffer from medication or disease-related adverse effects such as hyperlipidemia, peripheral neuropathies, depression, and others. Many of these conditions can be managed symptomatically and in consultation with an HIV specialist. In terms of the therapeutic management of HIV disease itself, the complicated nature of the disease and drug therapies is best managed by providers and care teams with specialized expertise in this area. This is underscored by the serious consequences and implications on future pharmacotherapeutic options that can occur if drug therapy is mismanaged.

There are currently five classes of antiretroviral drugs available for treatment of patients with HIV infection (Table 2). Each of these classes of medications acts to inhibit a specific process in the HIV replication cycle. The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of antiretrovirals to be introduced. The NRTIs act to inhibit HIV replication by binding to reverse transcriptase and halting viral DNA synthesis. The nucleotide reverse transcriptase inhibitors are structurally distinct when compared to the nucleoside reverse transcriptase inhibitors and require a lesser extent of intracellular activation, potentially increasing this class of drug's potency and making them less amenable to resistance. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) act in a similar fashion to

Table 2 Antiretroviral Agents

Generic	Abbreviation	Dosing	Trade Name	Adverse Effects
Nucleoside reverse transcriptase inhibitors				
Bind to and inhibit the enzyme responsible for the conversion of viral RNA to viral DNA.				
Zidovudine	AZT	300 mg PO BID	(Retrovir®)	Marrow suppression
Didanosine EC	ddI EC	400 mg QD	(Videx EC®)	Pancreatitis Peripheral neuropathy
Stavudine	D4T	40 mg BID	(Zerit®)	Peripheral neuropathy
Lamivudine	3TC	150 mg BID or 300 mg QD	(Epivir®)	Nausea,vomiting
Emtricitabine	FTC	200mg QD	(Emtriva®)	Headache, diarrhea
Abacavir	ABC	300mg BID	(Ziagen®)	Hypersensitivity reaction, rash
Abacavir	ABC	300mg BID	(Ziagen®)	Hypersensitivity reaction, rash
Zidovudine	AZT	1 Capsule BID	(Combivir®)	Marrow suppression
Lamivudine	3TC			Peripheral neuropathy Pancreatitis
Zidovudine	AZT	1 Capsule BID	(Trizivir®)	Marrow suppression
Lamivudine	3TC			Peripheral neuropathy
Abacavir	ABC			Hypersensitivity reaction, rash
Emtricitabine	FTC	1 Tablet QD	(Truvada®)	Diarrhea, nausea, vomiting
Tenofovir	TF			
Lamivudine Abacavir	3TC ABC	1 Tablet QD	(Epzicom®)	Nausea, vomiting, hypersensitivity reaction, rash
Abacavir	ABC			
Nucleotide reverse transcriptase inhibitors				
Bind to and inhibit reverse transcriptase enzyme; structurally distinct from NRTIs.				
Tenofovir DF		300mg QD	(Viread®)	Diarrhea, nausea, vomiting, nephrotoxicity
Non-nucleoside reverse transcriptase inhibitors				
Bind to and inhibit reverse transcriptase enzyme; structurally distinct from NRTIs.				
Nevirapine		200mg qdX2 weeks, then BID	(Viramune®)	Rash, diarrhea, hepatitis
Delavirdine		400mg TID	(Rescriptor®)	Rash, headache
Efavirenz		600mg Qhs	(Sustiva®)	Rash, CNS disengagement
Etravirine		200 mg BID	(Intelence®)	Rash, diarrhea

Table 2 (continued)

Generic	Abbreviation	Dosing	Trade Name	Adverse Effects
Protease inhibitors				
Bind to and inhibit protease enzyme. Protease enzyme normally cleaves and activates HIV pro-proteins.				
Saquinavir (Hard gel)		500mg BID (boosted)	(Invirase®)	Nausea, vomiting, diarrhea
Ritonavir		600mg BID	(Norvir®)	Multiple drug interactions, GI distress, perioral tingling
Indinavir		800mg Q8h	(Crixivan®)	Nephrolithiasis, increased bilirubin
Nelfinavir		1250mg BID	(Viracept®)	Diarrhea, nausea
Fosamprenavir		700mg BID (variable)	(Lexiva®)	Nausea, vomiting, diarrhea
Lopinavir/Ritonavir		2 Capsules BID	(Kaletra®)	GI upset
Atazanavir		400mg QD	(Reyataz®)	Increased bilirubin, decreased lipids
Tipranavir		500mg BID (boosted)	(Aptivus®)	GI upset
Darunavir		600 mg BID (boosted)	(Prezista®)	GI upset
Receptor antagonists inhibitors				
Prevent receptor medicated fusion between HIV and CD4+ cell receptors.				
Enfuvirtide		90mg SQ BID	(Fuzeon®)	Injection site reactions
Maraviroc (CCR5)		150 mg PO BID (varied)	(Selzentry®)	Cardiovascular, increased risk of malignancy?
Integrase inhibitors				
Bind and inhibit the integrase enzyme. Integrase is responsible for the integration of viral DNA into host cell DNA.				
Raltegravir		400 mg PO BID	(Isentress®)	Diarrhea, N/V
Multi- class combinations				
Emtricitabine Tenofovir Efavirenz	FTC TF Sustiva®	1 Tablet Qhs	(Atripla®)	Diarrhea, nausea, vomiting, CNS disengagement

inhibit viral DNA synthesis but do not become incorporated into the growing viral DNA chain. Protease inhibitors (PIs) are powerful antiretrovirals that inhibit HIV replication by binding to viral proteases and preventing the proteolytic activation of HIV polyproteins. Enfuvirtide is the sole commercially available fusion inhibitor, and it acts to inhibit HIV by preventing receptor-mediated binding of the virus to $CD4^+$ cells. While efficacious, the drug is limited by its high cost and subcutaneous route of administration. Recently, two new classes of antiretroviral drugs have been introduced (e.g., co-receptor antagonists and integrase inhibitors). Currently only

one drug is available in each of these two new classes. Maraviroc (Selzentry®) is a CCR5 receptor antagonist intended for use in patients who are treatment experienced [22, 23]. Maximum efficacy of the agent would be expected in cases of infection with a CCR5-specific strain of HIV. Therefore, a tropic assay to determine the co-receptor specificity of any particular strain is required prior to use of the drug [24]. Research and development toward the integrase class has been ongoing for several years and was previously hindered by the significant adverse effects often encountered by experimental agents in this class. Raltegravir (Isentress®) represents the first and only integrase inhibitor. Similar to maraviroc, raltegravir is intended for use in treatment-experienced patients. The drug has few interactions and a very favorable side effect profile [25].

The initiation of antiretroviral therapy in newly infected patients is undertaken on a case-by-case basis with tailoring to the patient's medical condition, desire for therapy, ability to adhere to complex medical regimens, and co-morbid conditions. Generally, therapy should be initiated when the $CD4^+$ cell count falls below 350 cells/mm^3 [5]. Previously viral load values had been a consideration for the initiation of therapy; however, $CD4^+$ cell counts are now considered the most critical parameter.

Furthermore, ongoing studies are underway to determine if initiation of therapy at higher $CD4^+$ counts may be associated with better outcomes. Clinical guidelines for the management of HIV also stress quality-of-life issues surrounding the initiation of antiretroviral therapy [5]. Antiretroviral therapy may be associated with significant adverse effects that contribute to overall morbidity. Decisions about when it is appropriate to initiate antiretroviral therapy should always involve patient-specific factors. Current consensus regarding the initiation of therapy focuses on preserving quality of life by balancing starting medications at a point where immune function is maximally preserved with consideration of side effects, lifestyle impact, and costs.

The efficacy of antiretroviral drug regimens is monitored using viral load assays. Viral load is a method of quantifying viral burden by measuring the number of circulating viral RNA strands in the bloodstream. Standard viral load testing has a lower threshold of 50 copies/ml, below which test results will be reported as "undetectable." Standard viral load testing can be performed by one of two methods: polymerase chain reaction (PCR) or branch chain DNA (bDNA). Because these two methods can produce differing results, the same testing method should be used consistently in any given patient. An undetectable viral load is a reflection of good viral control; however, it does not indicate that a patient is "cured" or no longer contagious.

Early in the epidemic, antiretroviral monotherapy was considered the standard of care in the management of HIV. However, because of the rapid development of resistance, monotherapy has been shown to result in inadequate and even detrimental effects. Current standard of care advocates the use of potent multi-drug combinations [5]. Most commonly these combination regimens are composed of two NRTIs and one PI or two NRTIs plus the NNRTI efavirenz. Once combination antiretroviral therapy is initiated, the goal of treatment should be an undetectable viral load (<50 copies/ml) [5].

Research has shown that the development of antiretroviral resistance is significantly less likely to occur when patients achieve and maintain undetectable viral loads [5, 26]. In cases where a previously undetectable viral load has increased or where viral load is unresponsive to therapy, patients should be started on a new multi-drug regimen, ideally composed of antiretrovirals to which the patient is treatment naïve. When patients have exhausted all standard regimens, clinicians should consider "salvage therapy" with fusion inhibitors or various alternative drug combinations. Addition of a single new additional 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 for the offending agent with another drug of the same class [5]. Drug doses should not be adjusted in response to adverse effects except in cases of renal insufficiency.

The success of current and future combination antiretroviral therapy is highly dependent upon patient adherence [27, 28]. Adherence is a challenge for many HIV-infected patients, due to various factors including pill burdens, drug costs, adverse effects, and lifestyle impacts. When initiating antiretroviral therapy and selecting specific drug regimens, clinicians should consider potential changes to the patient's current lifestyle as well as the quality of life [5]. In counseling HIV-infected patients, clinicians should be especially certain to emphasize the importance of strict adherence to prescribed regimens. Clinicians should also be prepared to offer practical advice and suggestions to enhance the understanding and adherence of HIV-infected patients.

Drug interactions are a concern when managing this patient population. Interactions which might result in sub-therapeutic antiretroviral drug concentrations should always be considered as they may result in the premature development of resistance. Management of drug interactions in HIV-infected individuals is a particular challenge because of the large numbers of medications used for the management of the virus itself as well as for the prophylaxis and treatment of opportunistic infections. Appropriate references should always be consulted to identify and evaluate potential drug interactions in this population [5, 29].

Many patients placed on potent multi-drug antiretroviral regimens achieve and maintain undetectable viral loads. While sustained undetectable viral loads are achieved in large numbers of patients, it appears as though some level of virus remains dormant in lymph nodes, CNS tissue, and other stealth cellular compartments [30]. In cases where antiretroviral medications have been withdrawn, these previously dormant virions begin once again to actively replicate. Therefore, until further trials are completed, it is not feasible to discontinue antiretroviral medications even after long-term sustained undetectable viral loads.

Recognizing that most antiretroviral regimens require stringent adherence and may be associated with severe adverse effects, some researchers have experimented with the concept of structured treatment interruptions (STIs) of antiretroviral drug therapy. STIs involve planned and limited interruptions in antiretroviral drug therapy in patients with undetectable viral loads. Conceptually, STIs are based on a premise that drug discontinuation in a patient with controlled viremia may result in an "auto-inoculation" against HIV. Unfortunately, most trials examining the results of STIs

have not demonstrated any discernable efficacy in this regard and are associated with the risk of the induction of resistance and future treatment failures. Therefore, STIs are currently not a recommended therapeutic intervention.

The search for new and effective antiretroviral medications continues. Most of the research in this area has focused on developing new antiretrovirals which target receptors/co-receptors or unique viral enzymes such as integrase. Efforts have also been made to simplify existing dosing regimens in order to enhance adherence [31, 32]. Examples of combination antiretroviral product intended to ease dosing are Truvada®, which contains 300 mg of tenofovir and 200 mg of emtricitabine per tablet, and Epzicom®, which contains 300 mg of lamivudine and 600 mg of abacavir per tablet. Perhaps the most significant recent addition to the antiretroviral armamentarium is the combination product Atripla®, which contains 300 mg of emtricitabine, 300 mg of tenofovir, and 600 mg of efavirenz per tablet. Atripla® represents the first single-dose, triple-drug tablet intended for the management of HIV.

8 Resistance Testing

A controversial issue in the management of HIV-infected individuals has been the role of antiretroviral resistance testing (Table 3) [27]. Antiretroviral resistance testing can be accomplished either genotypically or phenotypically. Genotyping relates resistance to either the presence or the absence of specific mutations at the genetic sites encoding for various HIV proteins including reverse transcriptase and protease. Phenotyping more closely resembles traditional antibiotic sensitivity testing

Table 3 Resistance testing: 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 the detection of 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

as it involves live viral cultures and varying drug concentrations. Many inherent limitations to resistance testing exist (i.e., cost, lack of interpretation guidelines, lack of laboratory standardization.). Despite these limitations, most clinicians agree that antiretroviral resistance testing should play some role in the management of HIV-infected patients. Clinical guidelines support the use of resistance testing in certain situations including use before initiating therapy in treatment-naïve patients and to manage cases of antiretroviral treatment failure [5]. There is no consensus on which assay (genotypic or phenotypic) should be employed by clinicians. The use of either test should be undertaken with an understanding of the limitations of each testing modality and the high cost of this technology. Phenotypic assays, which are more costly, might be better reserved for more complicated patients with extensive histories of antiretroviral exposure.

9 Conclusion

Since its first reported US cases in the early 1980s, clinicians and researchers alike have learned a great deal about HIV. AIDS has forced sensitive issues such as sexuality, discrimination, and death into the auspices of many clinical practices. As researchers continue the search for an effective cure, clinicians are helping seropositive patients lead healthier, more productive lives. The advent of potent antiretrovirals has dramatically changed the prognosis of this disease. Chronic management and longer life expectancies are now a reality; however, these are not without costs. Antiretroviral therapy often compromises quality of life and places tremendous financial burdens on patients. Therapy is always limited by the potential development of efficacy-compromising resistance mutations. Additionally, medications must be taken indefinitely as they do not represent a "cure." These advances have primarily been realized in industrialized nations, highlighting inequities around the globe. Even in the United States, the disproportionate impact of HIV/AIDS on minority populations reflects disturbing social disparities.

Complacency would likely result in a rapid return to the desperate situations often encountered in the late 1980s and the early 1990s. Research must continue in the area of drug and vaccine development. Effective and safe medications that inhibit novel enzyme targets will be needed if the advances seen over the last 20 years are to continue. Equally important, clinicians must continue to treat HIV-seropositive patients with empathy and caring, always considering the widespread implications of HIV disease on the patient's quality of life.

Key Points

- HIV is most commonly transmitted via sexual fluids, exposure to blood or bloody fluids, and via injection drug use.
- HIV infects and destroys $CD4^+$ cells, leaving patients susceptible to a number of serious opportunistic infections (OI). Prophylactic antibiotics are often employed to protect susceptible individuals from various OIs.

- Access to antiretroviral drug therapy in industrialized nations has resulted in fewer HIV-infected patients progressing to AIDS. Therapy typically involves the use of three concurrent antiretroviral agents.
- Antiretroviral therapy for HIV infection does not represent a cure, requires lifelong treatment, and has several limitations including high cost, multiple adverse effects, and a low ceiling to the development of resistance.
- As life expectancies of HIV-infected patients continue to increase, the provision of primary care to optimize overall health for these patients will become increasingly critical.
- Antiretroviral resistance is a common cause of treatment failure. Resistance can be delayed and/or prevented with stringent adherence to drug regimens. The presence of resistance can be detected through the use of either genotypic or phenotypic resistance testing.

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Part III
Special Considerations

Strategies for Optimal Antimicrobial Use

Arch G. Mainous III and Paul Little

1 Introduction

Optimalantimicrobialuse 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 payer, 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, 4]. In fact, in a recent double-blind placebo-controlled trial comparing placebo with the macrolides azithromycin and clarithromycin, it showed the direct effect of antibiotic exposure on resistance in the oral streptococcal flora in healthy volunteers [5]. Both macrolides significantly increased the carriage of macrolide-resistant streptococci compared with the placebo in these healthy adults.

The overall goal of reducing the prescribing of antibiotics should be an effort to minimize antibiotic resistance while appropriately delivering quality health care. There are some data to indicate that decreasing antibiotic use does lead to decreased resistance. In Finland, a nationwide reduction in the outpatient use of macrolide antibiotics resulted in a reduction of resistant group A streptococcus from 16.5 to 8.6% within 4 years. Practitioners were regulated to substitute macrolides for other antibiotics, and although macrolide use decreased, overall antibiotic use did not change [6]. Icelandic researchers have reduced the proportion of resistant pneumococcal infections through an intervention program delivered to patients and to the health-care team [7]. 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

A.G. Mainous III (✉)
Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: mainouag@musc.edu

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longer be effective, may become a reality. We will present a discussion of a variety of strategies that have been used to promote judicious antibiotic use.

1.1 Controlling Antibiotic Prescribing

In order to identify strategies to reduce antibiotic overuse and resistance, contributing factors must be understood (see Table 1). Overuse of antibiotics may relate to misinformation on the part of the practitioner and patient. For example, when presented scenarios that were consistent with an upper respiratory tract infection with discolored nasal discharge, the physicians, the pharmacists, and the patients were likely to prescribe, to recommend, and to desire antibiotics [8, 9]. Diagnostic and prognostic uncertainty may contribute to physicians prescribing antibiotics primarily for viral infections in order to cover the "chance" of bacterial infection or of complications. Clinical guidelines have been developed to improve diagnostic certainty with the hopes of therefore improving the management of common infections [10, 11]. Other strategies have focused on using biomarkers like C-reactive protein or procalcitonin to provide an indication as to whether an acute respiratory infection is likely to be viral or bacterial. In one trial, procalcitonin-guided therapy used as an adjunct to guidelines reduced antibiotic use without compromising patient outcomes [12].

As resolution of symptoms may serendipitously correlate with the course of antibiotics, patients' past use of antibiotics, for self-limiting illnesses, may also influence prescribing. 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

Table 1 Factors contributing to overuse of antibiotics

Contributing factor	Explanation
Experience	Provider: habit of antibiotic prescribing initiated in the pre-antibiotic resistance era
	Patient: perceived efficacy of prior antibiotic therapy for viral infections
Lack of education	Provider: suboptimal approach to diagnosis and treatment of common viral and bacterial infections
	Patient: belief that all infections require antibiotic therapy
Expectations	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	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

the doctor–patient relationship [13]. However, one study that examined the relationship between the amount of time spent by a physician in an encounter for a presumed viral respiratory infection when antibiotics are or are not prescribed showed no significant difference [14]. 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, create an increase in cost of care, and an increase in morbidity and mortality [15]. Several guidelines and clinical strategies have been published for optimizing antibiotic use and curtailing antibiotic resistance in hospitals [16, 17]. The Centers for Disease Control and Prevention have produced a wide variety of tools for preventing antibiotic resistance in health-care settings which provide guidance for hospitalized adults, for children, for long-term care, for surgical patients, and for dialysis patients (http://www.cdc.gov/drugresistance/healthcare/default.htm accessed on 2009). Although these guidelines must be tailored to each hospital system to target specific problems of antimicrobial resistance, local circumstances, and resources, there is some evidence that compliance with the guidelines will lead to lower levels of resistance [18].

1.2 Quality Improvement Initiatives

Over the past decade, numerous strategies have been implemented to curb antibiotic overuse. A recent systematic review of 55 separate trials indicated that broad-based interventions could have a community level impact on antibiotic use of 17–117 prescriptions per 1,000 person years [19]. Quality improvement efforts have been effective at reducing antibiotic use in ambulatory settings, but much room for improvement remains. The conclusion was that targeting all acute respiratory infections rather than single conditions in single age groups would have the greatest impact.

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 [19, 20]. Provision of drug-cost information in the computerized patient record has not been shown to affect overall mean prescription cost or prescribing patterns [21].

On the other hand, systematic reviews have documented that educational outreach visits, computerized and manual reminders, and interactive educational meetings (participation of health-care providers in workshops that include discussion or practice) are effective in promoting behavioral changes among health professionals [19]. Educational outreach visits, also known as academic detailing, use a combination of techniques to improve physicians' clinical decision making [22, 23]. Multifaceted interventions, which include a combination of audit and feedback, reminders, local consensus processes, and/or marketing are consistently effective interventions [19]. Point-of-care delivery of clinical guidelines and evidence-based recommendations has been shown to impact clinical practice [24]. Peer education (physician to physician) to improve quality of care and to reduce the cost of antibiotic prescribing was effective in office practices [25]. A multidisciplinary continuous improvement approach has been shown to increase clinical prevention efforts and to improve the delivery of diabetes care [26, 27]. Unfortunately, these more effective methods are not routinely used in medical education [28]. In a recent meta-analysis of continuing medical education trials, passive methods for disseminating information were shown to have a small impact on physician performance [29]. The most effective interventions are interactive, use multiple methods, and are designed for a small group of physicians from a single discipline.

Physicians and other health-care providers claim awareness of the problem of antibiotic resistance, which has been 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; these strategies include focusing on the system, on the provider, and on the patient (see Table 2). These strategies are often implemented in closed health-care systems and consist of tightly controlled interventions. However, when these interventions are applied to a less restrictive system and to a wider array of prescribers maintaining efficacy remains a challenge.

1.3 Antibiotic Control Policies

Clinical guidelines have been produced to control the use of antibiotics in hospital systems [16]. Antibiotic control programs are implemented in an effort to optimize antibiotic use while minimizing antibiotic costs [30]. 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 [15]. All team members must promote basic hospital infection control practices such as hand washing. Pharmacists and infection control teams are involved in monitoring drug use, in the surveillance and in the reporting of antimicrobial resistance patterns, and in the detection of patients colonized with potentially resistant and communicable bacteria. Antibiotic control

Table 2 Strategies to promote optimal use of antimicrobial agents

Administrative interventions	Denial of claims for inappropriate use
	Financial incentives and penalties
Antibiotic control programs	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	Computer-assisted management programs
Provider education	Academic detailing
	Peer education
	Local opinion leaders
	Interactive educational meetings
Patient intervention	Public/media campaigns
	Delayed prescription
Clinical guidelines	Locally developed with input from participating physicians
	Developed by an outside party (governmental agency, medical society, etc.)
Audit and feedback	Generated and delivered by members of the health-care team
	Generated and delivered by an outside party (e.g., governmental agency, health-care organization)
Multifaceted intervention	Quality improvement initiative involving educational interventions (to provider and patient), audit and feedback, etc.

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. A recent study examined the impact on antibiotic use in three different units of a hospital when guided by an infectious disease specialist [31]. Antibiotic consumption was recorded yearly from 1998 to 2005 in the three units. On Unit A, after approval by the head of the unit with the infectious disease specialist involved as a consultant upon request, restricted antibiotics were prescribed. On Unit B, restricted antibiotics had to be approved by an infectious disease specialist; all other antibiotics were prescribed by the physicians on the ward. On Unit C, all the antibiotics were prescribed by an infectious disease specialist. In Unit C, a significant decreasing trend in antibiotic consumption, in defined daily doses per patient day and per admission, and cost of antibiotics per patient was observed; in Unit B, a decreasing trend in antibiotic consumption per patient was also seen.

Antibiotic control policies are usually institutional interventions, creating barriers to inappropriate practices and limiting prescriber autonomy. Administrative interventions may also come from governmental agencies, which enforce specific practices by laws, by regulations, or by 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.

1.4 Computer-Assisted Decision Support

Integration of data from the microbiology laboratory, from the pharmacy, from the medical record, and from the financial databases can assist physicians to make decisions 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 and in an effort to improve antimicrobial prescribing, cost, and patient outcomes [32]. Electronic clinical decision support might help in both diagnosis and treatment decisions. Although, few studies have directly addressed the question of electronic decision support to improve antibiotic prescribing beyond a few small pilot studies, those studies suggest that clinical decision support may hold a particular promise [33, 34]. Recent data from a trial of a stand-alone personal digital assistant (PDA)-based clinical decision support system for the diagnosis and management of acute respiratory tract infections in the outpatient setting and overall adherence with an electronic decision support system for recommendations for the five most common diagnoses (pharyngitis, otitis media, sinusitis, bronchitis, and upper respiratory tract infection) were 82% [35]. When antibiotics were prescribed (in 53% of cases), adherence with the decision support system-recommended antibiotic was high (76%).

Antibiotic costs have been significantly reduced using a computer-assisted management program for antibiotics in a small intensive care unit [36]. 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-year intervention period, in 545 patients managed in the intensive care unit, there was a documented improvement in quality of patient care and in 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 them 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.

1.5 Provider Education

Many systematic reviews have shown that passive dissemination of information, or passive education, is generally ineffective in changing physician practice [19, 28]. 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 of intervention is more effective. Interactive educational meetings, where providers participate in workshops that include discussion or demonstration of skills, have been consistently effective [19]. 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, including assessment of baseline knowledge of each provider, identification of local opinion leaders, and use of positive reinforcement of improvements in clinical practice [23].

In a now classic study, investigators evaluated the effect of three educational methods on antibiotic prescribing in office practices in Tennessee [25]. 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 years 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 in patients receiving and in prescriptions for oral cephalosporins. Therefore, the intervention waseffective in improving the quality of care and in 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 [22, 37, 38].

The advantages of academic detailing programs and education outreach visits include the ability to tailor the discussion to the learner's level of understanding and to his or her 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. Since 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 the 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 but could potentially be addressed by interactive computer- or web-based systems.

1.6 Clinical Guidelines

Variation and uncertainty regarding the 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" [39]. 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.

The treatment of infectious diseases, like other common conditions, has been inundated with the development of clinical practice guidelines. In July of 2009, the National Guideline Clearinghouse, a public resource of the Agency for Healthcare Research and Quality listed 242 guidelines under the heading of bacterial infections and mycoses (http://www.guideline.gov/ accessed on 2009). Further, there were 81 guidelines just for respiratory tract infections. This mass quantity of guidelines makes it very hard for providers to be compliant, and they may become somewhat cynical of outside entities providing guidelines on which they are unfamiliar as a way to evaluate their practice patterns.

The impact of clinical practice guidelines has been disappointing and may be accounted for by the belief from physicians that they are not written for practicing physicians but rather focus on the current state of scientific knowledge [40]. 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 payers. The cost of developing and of 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).

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 days and to discharge patients within 4 days of hospitalization [41]. 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 on the patient outcomes.

In a Midwestern staff-model health maintenance organization, clinical guidelines for the treatment of uncomplicated cystitis were developed by local physicians and each clinical practice site determined their own process for guideline implementation [42]. The goal of the cystitis clinical practice guideline was to reduce treatment duration, to reduce the use of urine cultures, and 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, in nurse coordination of care, and in 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.

Sometimes, practice guidelines can have the unintended effect of modifying practice in a way that makes it difficult for providers to deliver care. One study examined emergency physician (EP) understanding of the Centers for Medicare and Medicaid Services (CMS) core measures for community-acquired pneumonia (CAP) guidelines and sought to assess the impact on their antibiotic prescribing patterns [43]. Nearly all of the physicians correctly understood the time-based guidelines for antibiotic administration, reported institutional commitment to meet these core measures, and stated that they had a department-based CAP protocol. Importantly, more than half of the respondents (55%) reported prescribing antibiotics to patients they did not believe had pneumonia in an effort to comply with the CMS guidelines. Only 40% of these physicians indicated a belief that the guidelines improve patient care.

With the rising concern of appropriate antibiotic use, there will inevitably be an increased number of clinical practice guidelines for infectious diseases. As practitioners, it will be important to evaluate their impact on the process of care, on the patient-care outcomes, and, more importantly, on the antibiotic resistance patterns. Advantages of using clinical practice guidelines in educational efforts include the ability to target those who need the education and the mostly the streamlining of care. 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.

1.7 Audit and Feedback

Audit and feedback, or any summary of clinical performance, has had variable success on promoting changes in physician behavior [19]. 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 and a comparison of this feedback 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 [40]. In order 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 [20]. Feedback on 2 years of prescribing was provided to more than two thousand practitioners, in two sets of graphical displays over 6 months. Prescribing patterns were compared to peer prescribing and were 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 [44]. 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 [45]. In their practice, they implemented a new system of care for otitis media including a patient handout, an 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-month 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 their practice culture and the internal development of a new system of care – which may be difficult to extrapolate to other practice settings.

When efforts to change are borne from within those requiring the change rather than imposed from 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 [40]. 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 successful audit and feedback interventions.

1.8 Delayed Prescriptions

Delayed antibiotic prescribing is one promising method of promoting judicious antibiotic use in primary care [46, 47]. Delayed prescribing refers to the strategy where a clinician provides an antibiotic prescription to be used by the patient but only if symptoms are not starting to settle in the time frame expected for the natural history or if symptoms are getting significantly worse during that time frame.

Systematic reviews 1:2 suggest delayed prescribing can reduce antibiotic prescriptions (with relative risk ranging from 0.25 to 0.54), which has been confirmed outside trial settings in a longitudinal observational study from primary care [11, 46, 48]. In a review of the six studies that supplied data on the proportion of patients who filled the antibiotic prescription, the post-intervention median rate of antibiotic use in the study control groups was 75% compared with 37.5% in the intervention groups [19]. However, the question arises why not just avoid prescribing antibiotics altogether when the patient presents with an apparently uncomplicated illness? There are two important reasons: First, we have relatively poor information about who is at risk of subsequently developing rare but important complications of infections – delayed prescribing is one way of providing extremely rapid access to antibiotics if symptoms are unexpectedly getting significantly worse (i.e., a rapid safety net). Second, the prescribing of antibiotics allows a ready compromise where there are very high patient expectations for antibiotics.

However, there are potential disadvantages of delayed prescribing. There is the possibility of mixed messages about the role of antibiotics – but if clear guidance is given about when to use antibiotics this should not be a great problem, since beliefs about antibiotics, when delayed prescribing is used, are very similar to beliefs when no offer of antibiotics is made [47, 49]. There are some data that suggest a decrease in patient satisfaction with delayed prescriptions [46]. If patients expect antibiotics and are denied them by their physician, then there are data to suggest that they can obtain them without a prescription [50, 51]. Thus, evidence-based guidance to patients is particularly important. A second issue is the possibility of an increased risk of complications. The data on clinical trials on delayed prescribing suggest complications are very rare. Patients should also be given clear advice about the natural history and the importance of returning if there are signs of developing complications.

1.9 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 [19]. 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 [40]. Second, there is no mandate of change in individual physician practice but rather a focus on the efficiency of delivery of care. Many health 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.

A large study that examined a multifaceted approach in the outpatient setting focused on improving the treatment of uncomplicated acute bronchitis in adults [52]. 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 (i.e., magnets, pamphlets, or 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 they 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 and 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 they were displayed in the patient examination rooms. The control sites provided usual care.

The study was conducted over a 3-month 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, during the study period, it did not change in the control or limited intervention site. Prescriptions for nonantibiotic medications (i.e., bronchodilators) did not differ among sites nor did return office visits for bronchitis or pneumonia. Therefore, in this focused intervention, antibiotic utilization for acute bronchitis improved in one office practice using a multifaceted intervention.

Ideally, using a multifaceted intervention that is 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. Furthermore, there have been few studies addressing the overall impact on patients – either symptomatic outcomes or the development of complications.

2 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 and in 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, delayed prescribing strategies, 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. Addressing antibiotic use and resistance is one of the most urgent priorities in confronting emerging infectious

disease threats [53]. 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, delayed prescription, 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.

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Infections in the Immunocompromised Host

Cristina Baker and Vicki A. Morrison

1 Introduction

Infection is one of the primary causes of morbidity and mortality in the immunocompromised host. Among those who are at greatest risk for infection due to defects in immunity are patients with cancer or HIV infection, neutropenic individuals, recipients of solid organ (SOT) and hematopoietic stem cell transplants (HSCT), and those whose underlying conditions require treatment with TNF-α inhibitors. Successful therapy for these conditions must be directed not only at managing the underlying disease but also at preventing and treating complications. In the following chapter, the predisposing factors and potential infectious complications of these disorders will be presented, as will the changing epidemiology of these infections. Finally, a general approach to prophylaxis and treatment of specific infections, including those caused by resistant organisms, will be provided.

2 The Cancer Patient

2.1 Fever in the Cancer Patient

Over two-thirds of patients with malignancy will have a fever at sometime during their clinical course. Fever in the cancer patient may occasionally be caused by the tumor itself. Malignancies most likely to cause fever include lymphoma, renal cancer, and hepatic cancer. About 10% of patients with metastatic disease, particularly those with liver metastases, may also have fever. More commonly, however, fever in the cancer patient is attributable to infection.

C. Baker (✉)
Staff Physician, Infectious Diseases, Hennepin County Medical Center, University of Minnesota, Minneapolis, MN, USA
e-mail: baker0088@umn.edu

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2.2 Immunodeficiencies and Associated Malignancies

Risk factors for infection in cancer patients are related both to humoral and cellular immune defects that are inherent to the primary disease process and to immunosuppression caused by therapy for the malignancy. Several hematologic malignancies have a characteristic spectrum of infection as a result of specific immune defects.

2.2.1 Chronic Lymphocytic Leukemia (CLL)

Patients with chronic lymphocytic leukemia (CLL) have a variety of immune defects, the most critical of which is hypogammaglobulinemia [1]. This deficit is more common and profound with advanced-stage disease and is not reversible by therapy, even with a concomitant hematologic response. The most common sites of infection are not only mucosal-lined surfaces, especially the respiratory tract, but also the urinary tract and skin/soft tissue.

Bacterial pathogens most frequently isolated in these patients include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and various enteric gram-negative organisms such as *Escherichia coli* and *Klebsiella pneumoniae*. Fungal (including *Candida* and *Aspergillus*) and viral infections (especially herpesviruses) are much less common, most often occurring in patients with advanced stage disease and/or chemotherapy-induced neutropenia. However, the introduction of purine analog therapy has altered the spectrum of infection because these drugs cause defects in cell-mediated immunity [2]. Pathogens seen in the setting of purine analog therapy include mycobacterial species, *Listeria*, *Nocardia*, *Aspergillus*, herpesviruses, and *Pneumocystis*.

2.2.2 Multiple Myeloma

Impaired humoral immunity is the hallmark of multiple myeloma (MM). Hypogammaglobulinemia is prominent in these patients, resulting from both decreased synthesis and increased catabolism of immunoglobulins. As in CLL, the immunoglobulin levels decline with disease progression. However, in contrast to CLL, an improvement in immunoglobulin levels may accompany a hematologic response to therapy. Humoral responses to immunization are also deficient in these patients. The mechanisms of these humoral immune defects are primarily related to impairment in the number and function of the residual polyclonal B cells.

Strep. pneumoniae and other encapsulated organisms such as *H. influenzae* and *Neisseria meningitidis* are commonly implicated in infection patients with multiple myeloma and fungal and viral infections are less frequent. Infections with enteric gram-negative organisms, *Candida*, and *Aspergillus* are common in the setting of neutropenia, most often occurring in heavily pretreated multiple myeloma patients and in those with extensive marrow involvement. As in CLL, there is a predilection for these infections to occur at mucosal surfaces.

2.2.3 Hairy Cell Leukemia

Cell-mediated immune defects, specifically T-lymphocyte dysfunction, are prominent in hairy cell leukemia. Quantitative and qualitative defects in granulocytes and monocytes are also present. Typically, infections are caused by common gram-positive and gram-negative bacteria and occur at mucosal sites and within skin or soft tissue. However, disseminated infections with not only opportunistic organisms – especially atypical mycobacteria – but also *Candida*, *Aspergillus*, *Pneumocystis*, and cytomegalovirus (CMV) are also seen, related to the monocytopenia that characterizes this disorder.

2.2.4 Hodgkin's Lymphoma

Patients with Hodgkin's lymphoma have underlying defects in cell-mediated immunity, predisposing them to infections caused by isolates such as *Listeria*, *Candida*, herpesvirues, and *Pneumocystis*. *Strep. pneumoniae* bacteremia may occur in the setting of prior, extensive combined-modality therapy or relapse. Lastly, in the small number of patients who now undergo staging laparotomy with splenectomy, infections caused by encapsulated organisms such as *Strep. pneumoniae*, *H. influenzae*, and *N. meningitidis* may occur, more commonly in children than in adults.

2.2.5 Myelodysplastic Syndrome and Large Granular Lymphocytic Leukemia

Neutropenia is common in myelodysplastic syndrome (MDS) and large granular lymphocytic leukemia (LGLL), the latter being a T-lymphocyte disorder. In patients with MDS, bacterial pneumonia and skin abscesses are common infections [3]. Recurrent bacterial infections, especially involving the skin, sinuses, and perirectal area, complicate the course of patients with LGLL. Organisms typically found in the setting of LGLL include *Staph. aureus* and *Pseudomonas aeruginosa*, with opportunists being less frequent.

2.3 Infection Based on Location of Malignancy

In addition to specific immune defects related to the primary disease process, the location of the malignancy may be crucial in predisposing to infectious complications. Obstruction of the respiratory tract, gastrointestinal (GI) tract, genito-urinary (GU) tract, and biliary tract by a tumor mass can result in infection. Central nervous system (CNS) dysfunction resulting from a primary or metastatic CNS tumor 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. Infections in these settings are most often caused by the usual colonizing organisms at that site. However, nosocomial infections, sometimes with multidrug-resistant organisms, are of great significance in hospitalized

patients and those patients receiving broad-spectrum antibiotic therapy with subsequent suppression of normal colonizing flora. In these settings, empiric treatment should be broadened to cover for potentially resistant organisms until culture results are available.

2.4 Infection Related to Treatment

Therapy administered for a malignancy can lead to additional immunosuppression. Cytotoxic chemotherapy may result in disruption of normal barriers to infection (skin, mucosa) or immune defects, including neutropenia, which has its own unique spectrum of infections (see next section). Specific chemotherapeutic agents, such as the purine analogs, result in T-lymphocyte defects that may persist for over a year after discontinuation of therapy. Corticosteroids used in the therapy of malignancies can cause qualitative defects in phagocyte and in monocytes/macrophages function. Radiation therapy can lead to damage of the normally intact, protective mucosal surfaces of the respiratory, GI, and GU tracts and to defects in cellular immunity. Alemtuzumab, used to treat CLL and lymphoma, results in profound defects in cellular immunity with significant reductions in B, T, and NK cells developing shortly after initiation of therapy and persisting for at least 9 months after discontinuation of treatment.

A variety of iatrogenic infections may arise in these patient populations. The placement of central lines for venous access or monitoring purposes, indwelling urinary catheters, and stents in obstructed regions such as the biliary tree may predispose to infection. Infections involving central venous access devices (CVAD) include local exit site infection, catheter tunnel infection, or catheter-related bloodstream infections. These infections are most commonly caused by staphylococcal species, with *Staphylococcus epidermidis* being the most frequent isolate in cases of catheter-related bacteremia. Integumentary defects from venipuncture, intravenous line placement, or bone marrow biopsy allow the introduction of colonizing skin flora, including nosocomial pathogens, past normally intact barriers, resulting in local or systemic infection.

2.5 Management of Infections in Cancer Patients

2.5.1 Antimicrobial Prophylaxis

Both preventive and therapeutic approaches to infectious complications have been examined in the cancer population. According to practice guidelines outlined by the National Comprehensive Cancer Network (NCCN), no bacterial or fungal prophylaxis is recommended for patients receiving standard chemotherapy for solid tumors and whose episode of neutropenia is expected to last for less than 7 days. Viral prophylaxis in this population is only recommended in patients with prior HSV episodes. In patients with hematologic malignancies such as CLL and multiple

myeloma that result in humoral immune dysfunction, bacterial prophylaxis is recommended. Updated guidelines for prophylaxis for the cancer patient can be found on the National Comprehensive Cancer Network website (www.nccn.org) [4].

2.5.2 Myeloid Growth Factors and Intravenous Immunoglobulin

Myeloid growth factors are advocated for use in cancer patients receiving myelosuppressive chemotherapy, which is likely to result in at least a 20% incidence of febrile neutropenia. The American Society of Clinical Oncology has devised guidelines for the optimal use of these agents for primary and secondary prevention of neutropenia [5]. Because of hypogammaglobulinemia present in some disorders, the use of immunoglobulin replacement has been examined, but studies have not supported its role in the therapy of established infections.

2.5.3 Antimicrobial Therapy

The general approach to antimicrobial therapy for infections in cancer patients should be based on an understanding of the underlying immune defects and corresponding predisposition for infections with specific organisms, as well as recognition of the local colonizing flora. Knowledge of local resistance patterns of nosocomial pathogens is important to consider, and clinicians should be aware of the hospital antibiograms for the institutions in which they practice.

2.5.4 Management of Catheter-Related Infections

Catheter-related infections are unfortunately common in patients with cancer. Whereas infection along the catheter tunnel generally requires catheter removal for cure, exit-site infections can 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, it may be necessary to remove the catheter to eradicate the infection, particularly if infection is due to isolates such as *Corynebacterium jeikeium*, *P. aeruginosa*, *Bacillus*, atypical mycobacteria, or *Candida* species. Guidelines regarding treatment of catheter-related infections have been established by the IDSA (www.idsociety.org) [6].

3 The Neutropenic Patient

3.1 Sources of Neutropenia

Myeloablative therapy is increasingly utilized for patients with various types of cancer. As a result, a larger proportion of cancer patients will experience at least one episode of therapy-related neutropenia, which may last from days to several weeks. Infection risk 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. The risk of infection rises with an ANC of less than 1,000/mm^3, but increases exponentially as the ANC declines to <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). At least one-half of the febrile neutropenic patients are found to have either an established infection or an occult infection. Over 20% of those with profound neutropenia (ANC < 100/mm^3) will be bacteremic. Signs and symptoms of infection may be masked in these patients, making infection diagnosis more difficult. A major factor in predicting a successful outcome from infection in the neutropenic host is recovery of the ANC.

3.2 Etiologic Agents of Infection

In addition to the skin, infections in neutropenic patients most commonly occur in the oral cavity, upper/lower respiratory tract, gastrointestinal tract, and perirectal area. The most common etiologic agents of infection are the organisms that normally colonize these sites. Use of broad-spectrum antimicrobial agents in these patients has an impact on the colonizing flora, with resultant eradication of the normal flora at mucosal sites, particularly anaerobes, and the potential for colonization and overgrowth by nosocomial and/or drug-resistant isolates such as methicillin-resistant *Staph. aureus* and vancomycin-resistant enterococci. The majority of bacterial infections in neutropenic patients are caused by enteric gram-negative (*E. coli*, *K. pneumoniae*, *P. aeruginosa*) and common gram-positive isolates (coagulase-negative staphylococci, *Staph. aureus*, α-hemolytic streptococci). Fungal infections are most frequently caused by *Candida*, followed by *Aspergillus.* Fluconazole prophylaxis may result in the emergence of isolates such as *Candida krusei* and *Candida glabrata*. Reactivation of HSV and other herpesviruses in HSCT patients is also seen.

3.3 Treatment

In the past three decades, much commentary has been published with regard to the antimicrobial approach in the neutropenic patient. In 1997, the first in a series of practice guidelines was commissioned by IDSA. The updated IDSA guidelines remain the best reference of the present recommendations for care in these patients (www.idsociety.org) [7]. 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 system compromise. Adjunctive therapy in the febrile neutropenic patient is also addressed in these guidelines. The use of empirical antiviral treatment, granulocyte transfusions, or myeloid growth factors is not routinely recommended.

4 Infections in the Hematopoietic Stem Cell Transplant Recipient

4.1 Immunodeficiencies Associated with HSCT

In the HSCT recipient, profound defects in cell-mediated and humoral immunity contribute to the increased risk for infection. Early in the post-transplant period, prolonged neutropenia occurs secondary to myelosuppression from the preparative regimen. Defects in both B- and T-lymphocyte function are pronounced in the allogeneic transplant recipient. Graft-versus-host disease (GVHD), as well as therapy rendered for this complication, results in increased immunosuppression, including subnormal immunoglobulin production and a hyposplenic state (with chronic GVHD). Lastly, the use of T-cell depleted marrow products results in pronounced and prolonged deficiencies in $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes. The use of peripheral blood stem cell products and the ancillary use of myeloid growth factors have been found to result in a shorter time to engraftment, thus a briefer period of neutropenia and less risk for infectious complications.

4.2 Etiologic Agents of Infection

There is a characteristic spectrum of post-transplant infectious complications in HSCT patients, related to the interval following transplantation [8]. The first month, post-transplant, is characterized by marrow aplasia with marked neutropenia. Integumentary defects, such as those from mucositis and CVADs, represent portals of entry for colonizing organisms. Total body irradiation, when utilized, results in additional cellular immune deficiency. Bacterial infections caused by various common gram-positive isolates (*Staph. aureus*, coagulase-negative staphylococci, viridans streptococci) and less commonly gram-negative enteric organisms predominate in this period. In patients who are seropositive for HSV, a high rate of reactivation may occur. BK virus reactivation can lead to bladder infection and hemorrhagic cystitis.

The spectrum of infection changes in the interval from 1 to 3 months, post-transplant, as engraftment with resolution of neutropenia has generally occurred by this time [9]. Acute GVHD may have its onset in allogeneic recipients during this period. Major pathogens causing infection during this time include CMV, adenovirus, *Aspergillus*, other non-*Candida* fungi, VZV, and human herpes virus-6 [10].

Following day 100, post-transplant, chronic GVHD may complicate the course of allogeneic transplant recipients. The incidence of pneumococcal bacteremia rises dramatically due to the functional asplenic state induced by chronic GVHD. Bacterial sinopulmonary infections, especially with encapsulated organisms, become more common. The incidence of VZV infections, mostly dermatomal, also increases. Infections with CMV and *Aspergillus* continue to occur through this phase [11].

4.3 Prophylaxis and Treatment

Prophylactic antimicrobial use in the HSCT population has been extensively studied [12]. Currently, the NCCN recommends that a fluoroquinolone, an anti-mold agent, and an antiviral agent be given as prophylaxis to all allogenic HSCT recipients. Because HSCT recipients who are CMV seropositive are at risk for CMV reactivation, the use of either CMV-negative or filtered blood products has been advocated in seronegative patients to prevent acquisition. In addition, prophylactic ganciclovir or preemptive ganciclovir therapy for patients identified as being at high risk for CMV disease by CMV antigen detection or polymerase chain reaction testing is recommended [13]. In the setting of autologous HSCT, anti-mold prophylaxis is only recommended in patients with mucositis. Following transplant, patients who have received alemtuzumab or have GVHD are generally given *Pneumocystis* prophylaxis. The NCCN has developed a complete set of guidelines for prophylaxis in HSCT patients (www.nccn.org).

Routine use of antimicrobial prophylaxis has led to the emergence of distinctive pathogens. Ubiquitous fluoroquinolone use has resulted in increased rates of infection with α-hemolytic streptococci and fluoroquinolone-resistant strains of *E. coli* and *P. aeruginosa.* Similarly, selective pressure due to fluconazole prophylaxis has resulted in an emergence of *Candida* species, such as *C. krusei* and *C. glabrata*, which are inherently resistant to fluconazole. Ganciclovir-resistant CMV infection also has the potential to become an increasing problem in HSCT recipients.

The approach to therapy of established infection is similar to that used for other highly immunocompromised hosts. Due to high rates of infection with drug-resistant organisms, selection of empiric antimicrobial therapy with activity against extended-spectrum beta-lactamase (ESBL)-producing organisms such as *K. pneumoniae*, *P. aeruginosa*, *Enterobacter cloacae*, *E. coli*, MRSA, and VRE should be considered in the appropriate clinic scenarios. Recovery of neutropenia is an important factor, affecting outcome especially with *Candida* and *Aspergillus* infection. Guidelines for the treatment of these infections were published by IDSA in 2003 and 2000, respectively [14,15]. The *Aspergillus* guidelines have been updated in 2008, to incorporate recommendations about newer drugs such as the echinocandins and new azoles (voriconazole, posaconazole).

5 Infections in the Solid Organ Transplant (SOT) Recipient

5.1 Immunodeficiencies in SOT Recipients

Due to defects in both cellular and humoral immunity, the course of SOT recipients is often complicated by infection. However, improvements in graft and patient survival and a decline in infection-related mortality have been seen related to better selection of candidates, progress in the regulation of chronic immunosuppressive

therapy, better selection of candidates, improved antimicrobial prophylaxis, and advances in surgical techniques. Cell-mediated immune defects predominate in the SOT recipient, further exacerbated by immunosuppressive therapy needed following SOT. Corticosteroids, though now used in lower dosages than in the past, result in defects in both cell-mediated and humoral immunity. Other immunosuppressive agents utilized, such as azathioprine, cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil, sirolimus, and monoclonal anti-T-cell globulins (OKT3, antithymocyte globulin), also result in significant and prolonged immune defects. Additional factors that contribute to the type, severity, and mortality of infection in the SOT recipient include underlying medical conditions (e.g., diabetes, hepatitis), the specific organ transplanted, and the duration of the surgical transplant procedure. The incidence of infection and subsequent mortality are lowest in renal transplant recipients and highest in the heart–lung recipients [16–18]. Liver transplant surgery has its own attendant complications, related to the length and technical difficulty of the procedure and anastomotic connections to nonsterile sites such as the biliary tree and intestine [19].

5.2 Etiologic Agents of Infection

The majority of infections following SOT occur within 4 months after solid organ transplant. However, a temporal sequence of infections in the post-transplant period has been recognized. Most infections in the first month, post-transplant, are either pre-existent preoperative infections (hepatitis), routine postoperative infections (pneumonia, wound or line-related infections), or HSV reactivation. Various infections are seen 2–6 months post-transplant. Bacterial infections may involve sites such as the bladder or sinuses. In addition, opportunistic organisms such as mycobacteria, *Nocardia*, *Listeria, Aspergillus*, *Cryptococcus*, CMV, *Toxoplasma*, and *Pneumocystis* may be implicated. In the period of greater than 6 months, post-transplant, three clinical groups with characteristic infectious complications are seen. Approximately 60–75% of patients require minimal immunosuppression and have good graft function at this time. Common infections such as respiratory tract infections, diverticulitis, and cholecystitis may occur in these patients but 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 related to long-standing immunosuppression, and these infections may lead to end-organ damage. Etiologies include BK and JC viruses (urethral stricture, hemorrhagic cystitis), hepatitis B or C (subacute or chronic hepatitis), Epstein–Barr virus (post-transplant lymphoproliferative disorders), CMV (especially retinitis), adenovirus, and VZV. The remaining 10–20% of patients who have poor allograft function and require large amounts of immunosuppressive therapy due to acute/chronic allograft rejection are at greatest risk of life-threatening opportunistic infections, with immunomodulatory viruses, such as CMV, being among the most common pathogens.

The etiologic agents of infection are somewhat dictated by the site of infection in the SOT recipient. Skin infections are commonly due to HSV and VZV, with *Papillomavirus* and various dermatophytes being less frequent. The skin may also represent a target organ for disseminated infection due to a variety of bacteria (including atypical mycobacteria), fungi, and viruses. The incidence of wound infections varies with the type of transplant and is particularly common in liver transplant recipients.

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 (TMP–SMX) prophylaxis, the incidence has now dropped to less than 10%. Common urine isolates include enteric gram-negative organisms, *Staphylococcus saprophyticus*, *Enterococcus*, and *Candida*. Less frequently isolated are *Mycoplasma*, *Mycobacterium* species, *Papovavirus* (BK, JC), and CMV.

Frequent sources of septicemia in transplant recipients are pathogens originating from the lung, GI or GU tracts, biliary tract, urinary tract, skin/soft tissue, and intravascular catheters. Polymicrobial bacteremia is not uncommon, especially in the setting of liver, pancreas, or small intestine transplants. Common isolates are enteric gram-negative organisms, *Enterococcus*, *Staph. aureus*, *Candida* species, and CMV.

A variety of pulmonary infections may arise, post-transplant. Community-acquired pneumonia may be caused by traditional organisms such as *Strep. pneumoniae* or other isolates such as respiratory syncytial virus. Although pulmonary tuberculosis may occur in these patients, many mycobacterial infections are disseminated. Etiologic agents such as *Histoplasma*, *Blastomyces*, and coccidioidomycosis need to be considered in endemic areas. Opportunistic infections with CMV, *Legionella*, *Pneumocystis*, and *Aspergillus* are also common.

Intra-abdominal infections are more problematic in patients who undergo transplant procedures involving the abdomen. *Candida* species may cause lesions throughout the gastrointestinal tract, as may CMV or HSV. Hepatitis may be viral in etiology (CMV, hepatitis C, VZV, HSV, adenovirus Type 5) or be a presentation of disseminated fungal infection (*Candida*, *Aspergillus*, *Histoplasma*). Liver abscesses and cholangitis may occur in the setting of biliary tract obstruction after liver transplant.

The greatest risk for CNS infection occurs in the first 4 months following SOT, although these infections 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 neurologic signs infrequently present. Pyogenic bacteria are uncommonly isolated, with opportunists such as *Listeria*, *Nocardia, Mycobacterium* species, *Aspergillus, Cryptococcus*, *Toxoplasma*, and *Polyomavirus* more frequently found.

Lastly, 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*. Nosocomial

outbreaks of infection also may occur, related to either the nosocomial flora at the transplant center or the water supply (as *Legionella* outbreaks).

5.3 Prophylaxis and Treatment

Prophylactic antimicrobial regimens are generally utilized in SOT patients. The most commonly used agent is TMP–SMX, which is typically given for a minimum period of 6 months following SOT. Not only does this provide prophylaxis for various urinary tract pathogens, it is also protective against organisms such as *Toxoplasma*, *Pneumocystis*, *Nocardia*, and *Listeria*. Unfortunately, the long-term use of TMP–SMX in this setting is a risk factor for the emergence of TMP–SMX-resistant *E. coli.* Ciprofloxacin may also be utilized for urinary tract prophylaxis, although its spectrum of coverage is more limited than that of TMP–SMX. Similarly, prophylaxis with ciprofloxacin in this setting has led to an increase in the rates of fluoroquinolone-resistant *E. coli*.

Although the use of isoniazid prophylaxis is controversial, it may be considered for patients with additional risk factors for active tuberculous disease, recent skin test conversion, or 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 for 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 intense, ganciclovir prophylaxis may be utilized to prevent CMV infection; alternatively, monitoring and pre-emptive ganciclovir may be used. Lastly, pre-transplant vaccination may be considered for pneumococcal infection, influenza, hepatitis B, and VZV, although data on the latter are limited. Typically, these vaccines are postponed during the first 3 months after SOT because the recipient is likely to have a poor immunologic response. No live virus vaccines should be administered following SOT due to immunosuppression.

With these prophylactic measures, awareness must be present as to the potential for development of drug-resistant isolates, which may be problematic in these immunocompromised patients. Drug-resistant isolates of importance in the SOT recipient are similar to those found in the setting of HSCT. When instituting broad-spectrum antimicrobial therapy in the setting of acute illness, coverage of bacterial pathogens – including extended-spectrum beta-lactamase (ESBL)-producing gram negatives – multidrug-resistant *P. aeruginosa*, VRE, and MRSA should be considered. Likewise, antifungal treatment with an echinocandin should be instituted if fungal infection is suspected in a patient on prophylactic fluconazole. Finally, if a systemic viral illness is suspected in a patient on prophylactic acyclovir or ganciclovir, the possibility of acyclovir-resistant HSV and/or ganciclovir-resistant CMV infection should be taken into account when selecting treatment.

6 Infection in the Patient with HIV/AIDS

6.1 Immunodeficiencies in Patients with HIV/AIDS

A wide range of immune system defects are associated with HIV infection. Aberrations in all branches of the immune system have been described, including dysfunction of T, B, and NK cells; neutrophils; and antigen-presenting cells. Disease progression and immunosuppression are primarily related to viral replication and subsequent damage to $CD4^+$ T cells. Before the development of antiretroviral therapy, the vast majority of AIDS-related deaths were due to opportunistic infections. Much of the early improvement in survival was due to the institution of *Pneumocystis* prophylaxis and management of opportunistic infections. Over the last two decades, the development of increasingly effective antiretroviral therapy has led to a dramatic decrease in infectious complications.

6.2 Etiologic Agents of Infection

The etiologic agents of infection in the setting of HIV infection relate to the level of immunodeficiency. The $CD4^+$ T-cell count is routinely used as a surrogate estimate of susceptibility to infection. At a $CD4^+$ T-cell count of less than 200 cells/mm^3, a patient is considered at increased risk for recurrent pneumonia (pneumococcus, *Pneumocystis*), oral candidiasis, and progressive multifocal leukoencephalopathy caused by JC virus. $CD4^+$ T-cell counts less than 100 cells/mm^3 lead to increased susceptibility to pathogens such as toxoplasmosis, *Cryptococcus*, and CMV. When the $CD4^+$ T-cell count drops below 50 cells/mm^3, the risk of infection with *Mycobacterium avium* complex is of concern. Other opportunistic infections that can occur at low $CD4^+$ T-cell counts include tuberculosis, endemic fungal infections (histoplasmosis, coccidiomycosis), cryptosporidiosis, worsening of chronic viral hepatitis, HSV, VZV, and human papillomavirus leading to warts on the anus, cervix, esophagus, penis, urethra, vagina, and vulva. Finally, patients with HIV are also at risk for complications such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and HIV-related encephalopathy.

6.3 Treatment

Opportunistic infections in patients with HIV infection may be challenging to manage because eradication is usually dependent on appropriate antimicrobial treatment and the use of antiretroviral therapy to control the virus and increase the $CD4^+$ T-cell count. As many HIV-positive patients are on multiple drugs, particular consideration must be given to interactions between antimicrobials and antiretroviral therapy leading to reduced drug efficacy or toxicity. Prophylaxis approaches are based on the patient's $CD4^+$ T-cell count. Standard of care includes the initiation of TMP–SMX

when $CD4^+$ T cells fall below 200 cells/mm^3 (dapsone or aerosolized pentamidine if sulfa allergic) and azithromycin at $CD4^+$ T cells less than 50 cells/mm^3. All patients with HIV infection should be screened for latent TB infection with a tuberculin skin test (TST). QuantiFERON testing should be used with caution in this population due to concerns about sensitivity of the test in immunocompromised persons [20]. As with a negative TST, a negative QuantiFERON test alone may not be sufficient to rule out TB in an immunocompromised host. Treatment for latent tuberculosis should be initiated for all HIV-positive patients with a tuberculin skin test reaction (TST) $\geq$ 5 mm or a positive QuantiFERON test. Current recommendations for infection prophylaxis and treatment are summarized by the United States Public Health Service and the Infectious Disease Society of America and are available at www.aidsinfo.nih.gov [21].

7 Infections in Recipients of TNF-α Inhibitors

7.1 Immunodeficiencies in Recipients of TNF-α Inhibitors

TNF-α inhibitors (adalimumab, etanercept, infliximab) are a relatively new class of drugs used to treat autoimmune diseases such as rheumatoid arthritis and Crohn's disease. By blocking TNF-α, these drugs lead to a reduction of inflammation in such patients. However, inhibiting this important cytokine leads to a disruption in the regulation of the immune system. Because TNF-α plays a central role in the formation of granulomas, treatment with these agents leads to an increased susceptibility to granulomatous infections.

7.2 Etiologic Agents of Infection

The most common pathogen reported with TNF-α inhibitor therapy has been *Mycobacterium tuberculosis*. Patients receiving TNF-α inhibitors are susceptible to new tubercular infection, as well as reactivation of old pulmonary and/or extrapulmonary disease. Infections caused by *Histoplasma, Aspergillus*, *Cryptococcus*, and *Listeria* have also been reported. In addition, severe bacterial infection with agents such as *Strep. pneumoniae* may occur in these patients.

7.3 Treatment

Before initiating therapy with TNF-α inhibitors, patients should be screened for latent TB infection. A tuberculin skin test (TST) or QuantiFERON test should be performed and isoniazid given for 9 months if the screening test is positive or if the patient has a history of a positive skin test or known exposure to an active TB case. In the event that a patient is thought to have significant immunosuppression,

the QuantiFERON test should not be used in place of the TST. There are no specific recommendations for prevention of fungal infection in these patients. Risk of infection, due to *Listeria,* may be attenuated by avoiding unpasteurized dairy products. Successful management in these patients requires a high index of suspicion for infection and regular clinical assessment.

8 Conclusion

Primary care physicians and physician extenders are able to manage most infections in the immunocompromised host. However on occasion, additional consultation is advisable. In the event that an infection is potentially serious or when problems occur with treatment, it may be necessary to consult an infectious diseases specialist. Specific instances in which additional consultation can be useful include treatment of multidrug-resistant organisms, management of infection control issues, and complicated, severe infections.

Key Points

- Knowledge of local resistance patterns of nosocomial pathogens is important to consider when treating immunosuppressed individuals.
- Catheter-related bloodstream infections caused by organisms such as *Staph. aureus, Pseudomonas, C. jeikeium*, atypical mycobacteria, or fungi require the removal of the catheter.
- Antimicrobial prophylaxis is warranted in almost all solid organ and hematopoietic stem cell transplant recipients for at least 6 months following transplantation.
- Antimicrobial prophylaxis to prevent opportunistic disease in those infected with HIV is based on the patient's CD4+ T-cell count.
- Patients being treated with TNF-α inhibitors are at high risk for tuberculosis and fungal infections.
- The benefits of broad-spectrum prophylactic medications in the immunocompromised patient must be weighed carefully against the propensity to select for resistant organisms.

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Future Trends in Antimicrobial Use

Arch G. Mainous III

1 Overview

The rapidly expanding challenge of antibiotic resistance impacts patients across the globe. Antibiotic-resistant organisms are becoming a massive clinical challenge in the twenty-first century. As outlined in the preceding chapters, all medical practitioners must be aware of the implications of drug resistance when prescribing therapy, as it is becoming very difficult to eradicate infections caused by these antibiotic-resistant pathogens. Pharmaceutical companies do not have vast new drugs in the pipeline. In many ways, we have come to the point as frightening as the preantibiotic era: For patients with multidrug-resistant bacteria, there is no magic bullet.

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 discuss several factors that contribute to the rise in resistant organisms and some potential new approaches to addressing this critical medical problem.

2 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 have shown no significant effect of antibiotics on purulent rhinitis or discolored nasal discharge [1]. In the treatment of acute bronchitis, the color of sputum is not

A.G. Mainous III (✉)
Department of Family Medicine, Medical University of South Carolina, Charleston, SC, USA
e-mail: mainouag@musc.edu

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related to the effectiveness of antibiotics [2]. 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 days in duration and accompanied by sore throat, cough, and runny nose with discolored (yellow, green, brown) nasal discharge, 79% of patients thought that antibiotics would be effective [3].

A lack of knowledge of appropriate use of antibiotics is not limited to patients; it also includes health care. 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 [4]. In scenarios of acute bronchitis, antibiotics were prescribed in 93% of cases with discolored sputum and 44% of those with clear sputum.

To decrease overuse and misuse of antibiotics, the practitioner prescribing of antibiotics needs to be impacted. A variety of interventions have been introduced to reduce unnecessary antibiotic prescribing [5]. These interventions include targeting specific populations or health systems as well as guidelines disseminated more generally. Some interventions have been effective but the impact could be improved. It would not be fair to assume that there has not been any headway in controlling overuse of antibiotics. Although initiatives in the general medical community may have been effective, they also have had some unintended negative effects related to development of resistant organisms. In a recent study examining antibiotic prescribing in outpatient settings in the United States between 1995 and 2002, antibiotic prescribing for respiratory infections, in which antibiotics would be rarely indicated, did exhibit a decrease; unfortunately, the proportion of broad-spectrum antibiotics increased significantly [6].

Physician education is still needed. Thus 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, thereby confronting the public health problem of antibiotic resistance. One novel and innovative strategy that is being investigated in several trials is the utility of electronic clinical decision support. By placing clinical decision support into an electronic health record or a personal digital assistant, the provider can be prompted with point of care questions and answers regarding diagnosis, treatment, and guidelines for care [7]. These decision support programs can give a provider an immediate, and potentially prompted, ability to see current guidelines as well as first- and second-line treatment options. Decision support for targeted prescribing of antibiotics should help decrease the inappropriate use of broad-spectrum antibiotics. Moreover, the Agency for Healthcare Research and Quality in 2009 began funding several trials to improve antibiotic prescribing for respiratory infections, thereby suggesting that evidence of new strategies will be available in the not-too-distant future.

A second strategy for reducing antibiotic usage is to encourage the development and use of vaccines. There are currently approved antibacterial vaccines

for pertussis, tetanus, diphtheria, meningococcus, pneumococcus, *Haemophilus influenzae*, cholera, typhoid, and anthrax. Successful development of vaccines is a time-intensive process [8]. Further, adherence to vaccine recommendations requires significant work but can be particularly effective. However, vaccines for streptococcal, staphylococcal, and other bacterial infections are being investigated. Following the demonstrated effectiveness of the *H. influenzae* type b (Hib) vaccine and *Streptococcus pneumoniae* vaccines, a group A streptococcus vaccine is being developed [9–11]. A group A streptococcus vaccine could have a significant impact on the use of antibiotics because even though guidelines and recommendations suggest testing for group A streptococcus before treating a sore throat, many physicians still treat empirically. Considering that there are more than 11 million physician office visits in the United States each year for pharyngitis, an effective vaccine should decrease the providers' suspicion of group A streptococcus and lead to decreased antibiotic prescribing for sore throats.

Similarly, we face an increasing threat from methicillin-resistant *Staphylococcus aureus* (MRSA). Recent data show that more than 50% of *S. aureus* isolates recovered in US hospitals are MRSA [12]. MRSA is continuing to appear in community samples. Consequently, a *S. aureus* vaccine would appear to have significant utility as another strategy to combat MRSA. Attempts to develop a *S. aureus* vaccine have been pursued for years. While some formulations have shown promise in ameliorating clinical disease, few, if any, of the *S. aureus* vaccines developed have adequately prevented new infection. Recent ongoing research is investigating a vaccine that appears to have significant promise for addressing MRSA, particularly community-associated MRSA. A large percentage of the community-acquired MRSA strains in the United States produce Panton–Valentine leukocidin (PVL), which is associated with severe infections. The new vaccine strategy targets the Panton–Valentine leukocidin, which appears to be an effective strategy [13]. As exciting as this research is on the new vaccine strategy, application to the general population is unfortunately something for the future, until the effectiveness and production can reach recommended levels.

Finally, an exciting new area of medicine is the potential modulation of the patient's own immune system which may provide alternative or adjunctive approaches to the use of antibiotics for the treatment of infectious diseases. Immunomodulation represents a novel approach therapy for infectious disease that depends on bolstering host immunity rather than direct antimicrobial activity. Immunomodulators can be divided into two categories: those that are specific to pathogens and those that are not specific to pathogens. Although few immunomodulators have been evaluated at this time, this strategy may become a significant one in this era of antibiotic-resistant pathogens [14]. 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 [15].

3 Migration and Lack of Regulation of Antibiotic Use

Initiatives to control antibiotic 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 2006 the estimated proportion of multidrug-resistant tuberculosis was 2.95 and 15.3% for new and previously treated tuberculosis cases [16]. This number can be misleading because the drug-resistant cases are not randomly distributed around the globe. In some Western European countries, there are essentially no multidrug-resistant cases of tuberculosis; however, in the former Soviet Union almost half of the tuberculosis cases were resistant to one drug and 20% had multidrug resistance. A recent study showed that clustering of multidrug-resistant tuberculosis cases in Europe was associated with origination in Eastern European countries [17, 18]. Perhaps not coincidentally, in a study of self-medication with antibiotics in 19 European countries, rates of self-medication were particularly high in Eastern Europe. Although over the counter sale of antibiotics is illegal throughout Europe, the acquisition of antibiotics from pharmacies without a prescription is common in Eastern Europe.

A risk factor for self-diagnosis and self-medication with antibiotics is the availability of drugs, and opportunity encourages use. Most initiatives regarding inappropriate direct human consumption of therapeutic antibiotics focus nearly exclusively on controlling prescribing by health-care providers. Corresponding estimates of the reservoir of antibiotics in the community are then based on evaluations of prescribing behavior.

In many countries, either antibiotics are 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 [19]. Data from many countries suggest that self-medication is common and frequently inappropriate [20, 21]. 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 which fulfilled the requirements for a single day's dose [22]. In a relatively affluent district of Manila, the Philippines, 90% of antibiotic purchases were for 10 or fewer tablets or capsules [21].

The process of migration and travel not only allows resistant organisms to move from an area with high use of self-medication with antibiotics but also allows for cultural norms regarding self-medication with antibiotics to travel from one area to another. Industrialized countries are not immune to the problem of self-prescription of inappropriate antibiotics. In a town on the US side of the US–Mexican border, 75% of the respondents had purchased prescription medications in Mexico without a prescription [23]. Even though the United States has strict regulations on the

dispensing of antibiotics without a prescription, recent evidence has shown that acquisition of antibiotics without a prescription is a common phenomenon in the Latino community in the United States [24, 25]. Approximately 20% of Latino residents in South Carolina have purchased antibiotics without a prescription in the United States.

Health beliefs and practices are integrated into one's ethnic and cultural orientation. Antibiotics are commonly available without a prescription in Latin American countries. Some belief systems that have roots in Latin American cultures may encourage the overuse of antibiotics and particularly the use of non-prescribed antibiotics. Latinos past experiences play a significant role in their practice of self-diagnosis and self-medication. In a study using focus groups, a US resident from Mexico said "If I already know my symptoms and what medicine heals me, I'm not going to go to the doctor so they can give me a prescription there. If I go, they'll charge me just for the visit, and then I have to go buy the prescription and that's more money, another cost. If I know what medication I'm going to take and will work for me, I'll go buy it and it's cheaper for me" [25]. Such entrenched beliefs are hard to change and will require considerable effort to control this potentially large pool of unregulated antibiotics.

A more concerning trend is that this phenomenon of acquisition of antibiotics without a prescription in a country with strict regulation may move from inconspicuous activities in ethnic neighborhoods to the larger general population. A recent study documented the phenomenon of selling antibiotics without a prescription on the Internet [26]. Some prescription medication is sold without the purchaser presenting a valid prescription which is a violation of the Federal Food, Drug, and Cosmetic Act. Other vendors attempt to circumvent this law by providing online diagnoses and prescriptions based on health histories without a physical exam and without an ongoing relationship between patient and physician, practices that are not considered appropriate standard of care.

In the study of Internet vendors, 138 unique vendors selling antibiotics without a prior prescription were evaluated. Penicillins were available on 94.2% of the sites, macrolides on 96.4%, fluoroquinolones on 61.6%, and cephalosporins on 56.5%. A total of 98.6% ship to the United States. The mean delivery time is 8 days with 46.1% expecting delivery in greater than 7 days. Among those selling macrolides ($n = 133$), 93.3% would sell azithromycin in quantities consistent with greater than a single course of medication. Vendors who sell antibiotics without a prescription are more likely to sell quantities greater than a single course and more likely to take more than 7 days for the antibiotics to reach the customer than those that require a medical interview. The above strategies of unregulated vendor sells of antibiotics encourage self-medication and low quality of care. Currently, it is unclear how many courses of antibiotics are sold on the Internet or how many people are using these sites but if left uncontrolled it could be a significant portal for unregulated antibiotics in the United States.

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. Substantial patient educational initiatives

coordinated across countries may be necessary. A key to controlling resistance requires cooperation and shared belief systems from patients, physicians, and others in the health-care system regarding appropriate treatment.

4 Use of Antibiotics in Household Cleaning Products

Concern has been growing over the use of antibacterial household and personal hygiene products as another factor contributing to antibiotic resistance [27]. There recently has been a proliferation of household products containing antibacterial agents. In particular, many contain triclosan, which has mechanisms for killing bacteria similar to many systemic antibiotics and which has other mechanisms that can confer resistance to antibiotics used to treat human disease [28]. One concern is that the use of these products contributes to an environment with low, sub-effective concentrations of antibiotics in the environment thereby contributing to the development of antibiotic-resistant organisms.

Currently, the results regarding the impact of antibacterial cleaning products on antibiotic resistance have been mixed. One study found bacterial contamination with pan-resistant *Acinetobacter* and *Klebsiella*, multidrug-resistant *Pseudomonas*, and MRSA on the surfaces of dispensers of hand soap with 2% chlorhexidine [29]. Gram-negative isolates could multiply in the presence of 1% chlorhexidine. In contrast, in a study in which households were randomly assigned to use either antibacterial or nonantibacterial cleaning and hygiene products for 1 year, the study did not find an increased risk with using antibacterial products [30]. Antibacterial product use did not lead to a significant increase in antibiotic resistance after 1 year nor did it have an effect on bacterial susceptibility to triclosan.

There is good evidence to suggest that high standards of hygiene in the home can have a significant impact in reducing the number of infections arising in the home. With an interest of consumers in reducing their risk of infections, there has been substantial growth in soaps and cleaning products with antibacterial ingredients. Because the relationship between antibacterial household products and antibiotic resistance is still unclear, some have called for the removal of antibacterial ingredients in these products where the mechanism of antibiotic resistance has been characterized [31]. Further examination of these cleaning products is warranted along with additional education of consumers of the potential role of certain ingredients on development of antibiotic resistance.

5 Expanding Use of Antibiotics in Nonmedical Settings: Animal Feed

As mentioned above in regard to antibiotics obtained without a prescription, rather than seeing the only reservoir of antibiotics that may lead to resistance as those coming from human prescriptions, other sources contribute to one large reservoir. 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. In agriculture, antibiotics are used as feed additives to promote growth and feed efficiency. Antibiotics from almost every clinical class are permitted for use in some country as feed additives. This agricultural strategy is found in the production of poultry, swine, cattle, and aquaculture. Prophylactic antibiotics are used "nontherapeutically" in healthy animals.

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) [32]. Other studies have found significantly higher prevalence of multidrug-resistant *E. coli* in animals supplied with antibiotics in feed as compared with those from organic farms [33]. Antibiotics added to animal feed not only reduce the normal intestinal flora which compete with the host for nutrients but 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 [34]. Although the quantity of antibiotics used in feed varies, the concentration is often referred to as "nontherapeutic." 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.

The resistant bacteria is exposed to humans through a variety of channels. First, it can be present in the meat that one consumes [35], making the actual consumer food product a possible route of exposure. Other routes include air, water, and soil near the food animal production facilities. The major source of resistant pathogens is via waste disposal, which can contaminate ground water and surface water as well as create contaminated dust. An additional source that has been recently identified is in food crops grown in soils irrigated with contaminated water that may be relatively distant from the initial food animal production facility. Resistant pathogens have been found on food crops irrigated with this contaminated water [36].

In terms of human disease risk, the use of antibiotics in agriculture creates a large reservoir of nonhospitalized individuals carrying resistant organisms. Consequently, when these individuals enter the hospital or health-care settings, they are often colonized and may be a major source of resistant infections thereby increasing the risk of antibiotic resistance in the health-care setting. A large number of people exposed to a low risk in the community setting may cause more cases of resistant infections.

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 [32]. The Hazard Analysis and Critical Control Point (HACCP) in the United States regulates the farm and the food consumers eat, but regulations are not very effective within or near the farm, which is where much of the waste contamination occurs. The HACCP places no regulation on food animal production to contain the risks of antibiotic resistance. Adherence to the World Health Organization recommendations [37] will ensure a

systematic approach toward replacing antimicrobial growth promoters with safer non-antimicrobial 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 [38].

The contribution of agriculture to the reservoir of antibiotic-resistant organisms is significant as well as the downstream consequences for public health, and so attention to this issue in the future is critical.

6 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, on infection prevention, and on vaccination is needed to further reduce the use of antibiotics. Public policy to support worldwide public health efforts to monitor and to respond to antibiotic resistance is critical, and a global perspective is necessary. New indications for antibiotic use in humans as well as 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.
- Future strategies to deal with infectious diseases and antibiotic resistance may include a greater emphasis on electronic clinical decision support, vaccines, and immunomodulation.
- Antibiotic resistance is a global problem that is exacerbated by migration and travel. Coordination of policies regarding regulation of antibiotics across countries is necessary to effectively deal with the problem.
- 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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Subject Index

The letters ‘f’ and ‘t’ following the locators refer to figures and tables respectively.

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