A Lippincott Williams and Wilkins
Handbook

Handbook of Antibiotics

Third Edition

Richard E. Reese
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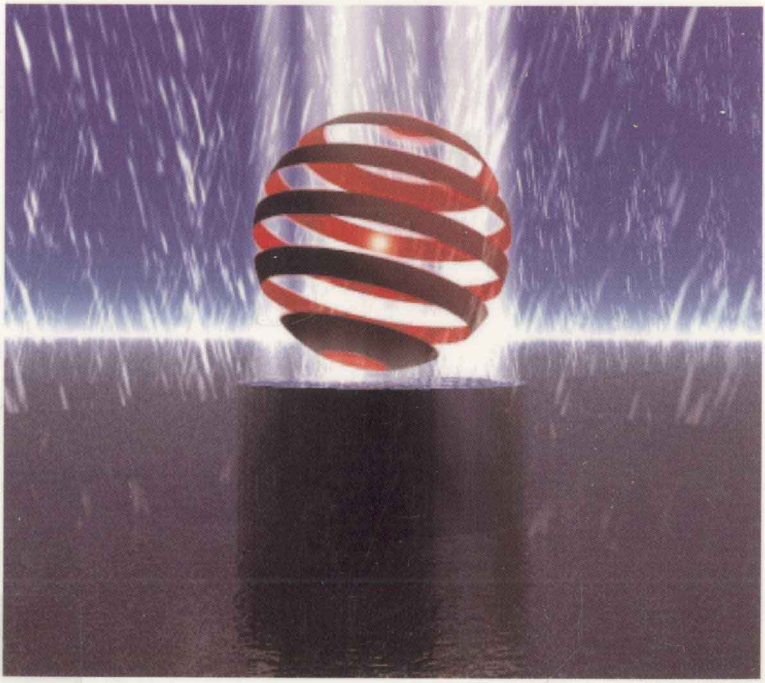

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Third Edition

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This book is dedicated to Ann Sullivan Baker, M.D.
Ann was an Associate Professor of Medicine
at Harvard Medical School, Physician on
the Medical Services of the Massachusetts
General Hospital,
and Director of the Infectious Disease Service at
the Massachusetts Eye and Ear Infirmary in Boston,
a good friend and colleague.

Preface

This book is intended for medical students, house officers, practicing physicians, physician assistants, and other health professionals involved in evaluating patients and prescribing antibiotics.

It is estimated that up to 50% of antibiotics prescribed in the United States are inappropriately used. Frequently, the antibiotic is not indicated. Often when it is indicated, the incorrect antibiotic is chosen, the dose is incorrect, or the duration is inappropriate for the clinical situation.

The *Handbook of Antibiotics* provides a concise discussion—not just a series of tables—of virtually all of the antibiotics currently in use, including the new antibiotics that have been approved in the last year. It has become increasingly difficult for the clinician to stay abreast of these new agents, especially with respect to their pharmacokinetics and their side effects. This handbook provides that necessary information to the practitioner in an easy-to-use outline format.

An additional important feature of this handbook is that concise discussions of common infectious diseases are provided. These discussions emphasize clinical reasoning as to when to use a standard antibiotic, or whether a newer agent is recommended. We hope that this approach, which is unique for a handbook, will help the clinician reduce the figure of 50% inappropriate antibiotic usage.

We believe that this material will be practical and useful. This is because the recommendations therein are based on a combined 50 years of patient care, as well as answers to challenging questions posed by clinicians at all levels of training and experience. Furthermore, from these interactions we have modified this text in response to helpful suggestions, thus speaking to the needs of the users.

After the success of the first edition (1983) and second edition (1986) of *A Practical Approach to Infectious Diseases,* many suggested that we publish separately its section on antibiotic agents. The fourth edition of *A Practical Approach to Infectious Diseases* was published in 1996. This third edition of the *Handbook of Antibiotics* is, in part, a concise update of the antibiotic discussions of that text and a discussion of the initial considerations and management of common entities (e.g., sepsis, pneumonia, URI, UTI) in Part I. The discussion of specific antibiotics follows in Part II.

We thank Mary Muller and the personnel at the Text Processing Department at Bassett Healthcare, Cooperstown, New York, for their help in typing and preparing this text; Linda Muehl, librarian, for her tremendous help in doing multiple literature searches; and Joseph S. Bertino, Jr., Pharm.D., Michael A. Foltzer, M.D., and Alan J. Kozak, M.D., at Bassett Healthcare for their useful advice. One of the authors (R.E.R., who was at Bassett Healthcare until late 1999) thanks Walter A. Franck, M.D., Physician-in-Chief at Bassett Healthcare, for his encouragement and support of this writing project.

In addition, we thank all those at Lippincott Williams & Wilkins who aided in the fruition of this book. Finally, we thank our wives, Shirley, Sherrill, and Betsy, for their patience, encouragement, and support during the preparation of this text.

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Contents

PART I

Common Infections

1

Upper Respiratory Infections and Influenza

Approximately 20 million office prescriptions per year in the United States are written for upper respiratory infections (1,2). The most common diagnoses are otitis media, nonspecific upper respiratory tract infections (URIs), bronchitis, pharyngitis, and sinusitis (1). These infectious accounted for more than 75% of prescriptions written annually in physicians' offices (1). Therefore a practical approach to these common problems is essential.

I. **Clinically relevant pathophysiology of URIs.** The **"common cold"** usually involves the sinuses.
   A. **Computed tomographic (CT) changes.** An important study documented that rhinovirus-induced **common colds are associated with CT abnormalities of the sinuses in more than 85% of cases** and these abnormalities resolve without antibiotics! Therefore **the common cold is really a viral rhinosinusitis** (3), not just a rhinitis (4).
   B. **Mucopurulent rhinitis** (thick, opaque, or discolored nasal discharge) **frequently develops 1 to 3 days after the onset of the common cold** because nasal secretions contain desquamated epithelial cells, polymorphonuclear cells, and nonpathogenic bacteria that normally colonize the upper respiratory tract (4).

      This is not an indication of bacterial infection and thus is not an indication for antimicrobial treatment (4).

II. **Excessive outpatient antibiotic use.** Even though antibiotics do not affect the clinical course of uncomplicated viral illness, recent studies have emphasized that **common viral respiratory tract infections** are **often inappropriately treated with antibiotics** in both adults and children. More than 40% to 50% of children and adults with common colds or URIs, and more than 60% to 70% of children and adults with bronchitis with no underlying lung disease receive unnecessary antibiotics (2,5). As discussed later in this chapter, antibiotics are also often unnecessarily prescribed for children with the common findings of asymptomatic otitis media with middle ear effusions (6).

III. **Problems from excessive antibiotic use.**
   A. **Increasing bacterial resistance.** Excessive use of antibiotics in ambulatory practice has contributed to the emergence of antibiotic-resistant bacteria in our communities (1,2,6,7). It is especially worrisome if antibiotics are often not even indicated, as in uncomplicated viral respiratory infections, and yet still used.

      Now more than 30% of respiratory isolates of *Streptococcus pneumoniae* isolated are penicillin resistant. (See detailed discussion of this issue on pages 326–330.)

This has complicated the antibiotic decision-making process especially in acute otitis media (AOM) and community-acquired pneumonia (Chap. 2)

B. **Unwanted side effects.** Patients treated with antibiotics for viral infections "gain" only the side effects associated with those antibiotics along with the considerable out-of-pocket or out-of-insurance-fund expense. Many patients are now admitted with severe *Clostridium difficile* colitis or severe drug rash or drug fever that costs them time lost from work and the health care system excess expense. Once allergic to one class of antibiotics, alternative agents used in the future may be more expensive or broader in spectrum than clinically necessary.

IV. **Why do physicians overprescribe antibiotics,** especially in the ambulatory setting (7–9)?

A. **Insufficient time** to discuss with patients/families why an antibiotic is not really needed is a consequence of pressure to see patients in a shorter period of time. With pressures to see more patients, writing a prescription is easier than explaining why an antibiotic should not be used. See Sec. II.

B. **Lack of understanding of the natural history** of viral respiratory infections and acute otitis media (AOM) with effusion contributes.

C. **Clinician experience and patient experience and/or expectations.** When a clinician does not care for children as often as adults, the physician may be more inclined to use antibiotics for URIs. When a child or adult has received antibiotics for a similar illness in the past, that experience raises his or her expectations for antibiotics (8).

D. **Economic pressures** are poorly studied but are probably very important. Concerns about patient/parent satisfaction and retention are often cited as reasons for using antibiotics. In managed-care settings, physicians may believe antibiotics may reduce the likelihood of return visits for URIs.

V. **Possible approaches** (7,9)

A. **Physician education** about the pathogenesis of common URIs and the judicious use of antibiotics is essential.

1. **Education must begin in medical school/house staff training.**
   a. Data on the pathogenesis of these infections and appropriate use of nonsteroidal antiinflammatory drugs (NSAIDs) and antihistamines should be provided (see later discussions).
   b. Education must emphasize lack of efficiency in viral infections, frequency of side effects, and increasing incidence of bacterial resistance.
2. **In pediatrics,** an excellent series on important principles for judicious use of antibiotics has recently been published (6). Essential points of this

supplement are summarized in the discussions that follow.

3. **In adults,** fewer published guidelines are available but the pharyngitis guideline (10) is discussed below. More guidelines are needed.

B. **Education of the general public** is as important as physician education (7,9).
   1. **Materials that** help **explain** the potential **harm** of **unnecessary** use of **antibiotics** are available for pediatric patients and **should be used regularly.*** Brochures are being developed for use in adults. One reviewer emphasizes: "Parents are busy and want their children well yesterday" (9).
   2. **Physicians need to educate the public** about the appropriate use of antibiotics (e.g., at community meetings, with newspaper columns, etc.).
   3. The media and medical community need to reach the general population about the benefits of anti-inflammatory drugs and first-generation antihistamines' role early in cold symptoms. See Sec. I.D. under "The Common Cold."

C. **Economic pressures must be refocused** to promote more judicious use of antibiotics (8). Managed-care administrators must be made aware that management policies that indirectly encourage antibiotic overuse are, in the long run, not cost-effective. Increased costs from unnecessary prescriptions, adverse drug reactions, and treatment failures in patients with antibiotic-resistant infections must be weighed against the perceived benefits of therapy (8). These topics need further clinical study and input from national organizations expert in antibiotic use.

Nasopharyngitis (the Common Cold)/ Upper Respiratory Infections (URI)

I. **Background.** As previously discussed, the common cold is really a rhinosinusitis (3,4).
   A. **Acute illness** is characterized by rhinorrhea, sneezing, sore throat, cough, and in children, low-grade fever.
      1. Children may have three to eight colds per year (4).
      2. Adults typically have one to three colds per year.
   B. **Etiology.** Rhinoviruses and coronaviruses account for the majority of infections in children; rhinoviruses are especially important in adults.
   C. **Course**
      1. The **usual duration is 3 to 7 days** with peak symptoms on the second and third days.

* See pamphlet "Your Child and Antibiotics: Unnecessary Antibiotics Can Be Harmful," prepared by the American Academy of Pediatrics, Centers for Disease Control and Prevention, and American Society for Microbiology.

2. **Mucopurulent rhinitis (thick, opaque, or discolored nasal discharge) frequently develops and is not an indication for antimicrobial treatment, as discussed earlier (4).**

D. **Therapy**

1. **Antimicrobial agents should not be given for the common cold.** Controlled trials of antimicrobial treatment of the common cold have consistently failed to show that treatment changes the course or outcome (4).

   Antimicrobials should not be given "to prevent bacterial complications" of the common cold since this is not an effective strategy (4).

2. **Symptomatic therapy**

   a. **Naproxen,** a NSAID, in a randomized, double-blind, controlled trial of experimental rhinovirus colds in young adults had a beneficial effect on the symptoms of headache, malaise, myalgia, and cough (11). Virus shedding was not altered. Prostaglandins may be among the inflammatory mediators that play a role in the pathogenesis of rhinovirus colds (11) and presumably other viral colds. Presumably, other NSAID may have a similar effect.

   b. **First-generation antihistamines.** Although early studies suggested the role of antihistamines in the therapy of common colds was controversial (12), recent studies suggest a potential benefit of early initiation of first-generation antihistamines in adults. **Clemastine fumarate** reduces sneezing and rhinorrhea (13). Likewise, **brompheniramine maleate** (e.g., the antihistamine in Dimetapp) was efficacious in reducing sneezing, rhinorrhea, and cough associated with rhinovirus colds (14). Mild drowsiness, dry mouth, and dry throat are potential side effects in a minority of patients.

      The role of antihistamines in children awaits further study.

   c. **Intranasal ipratropium bromide (Atrovent)** has been shown to provide specific relief of rhinorrhea and sneezing with common colds in adults in a randomized, double-blind, placebo-controlled trial (15). These studies have been done in patients more than 12 years old, and the nasal spray was used for 4 days.

   d. **Pseudoephedrine plus acetaminophen** when given to subjects who had cold symptoms for less than 48 hours caused improvement of "sinus" pain, pressure, and congestion when compared with controls in a preliminary report. The combination was well toler-

ated, except that 4% of the pseudoephedrine-acetaminophen subjects complained of nervousness (15A).

e. **Symptomatic therapy.** Acetaminophen in children and acetaminophen or aspirin in adults has been used. If a NSAID is used (Sec. a), we would avoid also using aspirin. Cold water vaporization has been used.

f. The use of antihistamines and oral decongestants has been advocated for treating children in an attempt to prevent AOM. However, these agents were initiated too late to be effective, and at that point, such therapy has not been beneficial. Further studies need to be done in this area.

3. **Complications.** In children, **AOM** or **bacterial sinusitis** may follow a cold and merit antibiotics; this is also true in a small proportion of adults with bacterial sinusitis. See specific later discussions of these entities.

E. **Transmission** is from person to person, requires close contact, and probably involves transfer of the virus from the hands of an infected person to an intermediate surface or directly to the hands of a susceptible person. **Therefore good handwashing can help prevent the spread of these viral infections.**

Acute Pharyngitis and Tonsillitis

The management of acute pharyngitis is an area of ongoing discussion. At any age, **the majority of cases** of pharyngitis (usually >70%) are not exudative, and **usually are due to viruses.** Group A beta-hemolytic streptococci (*Streptococcus pyogenes*) are the major cause of bacterial pharyngitis (particularly exudative tonsillitis), which is the only commonly occurring form of acute pharyngitis for which antibiotic therapy is definitively indicated. **Antibiotic therapy is advised (10) for group A streptococcal (GAS) infection** to (a) prevent the suppurative complications (e.g., peritonsillar abscess); (b) prevent nonsuppurative complications (e.g., rheumatic fever); (c) decrease infectivity to reduce transmission to family members, classmates, and close contacts and allow the rapid assumption of normal activities; and (d) prevent rare cases of invasive streptococcal syndromes. Controlled studies have demonstrated a slightly shorter duration of clinical illness as well.

Antimicrobial therapy is not of proven benefit in the treatment of acute pharyngitis due to bacteria other than GAS infection, with the exception of very rare infections due to *Corynebacterium diptheriae* (diphtheria) and *Neisseria gonorrhoeae* (10).

I. **Clinical presentation. No reliable predictive model based on clinical signs and symptoms exists to identify all individuals with streptococcal pharyngitis (10).**

A. The **"classical" clinical features of acute streptococcal pharyngitis** are the following: onset in winter or spring; school-age child; abrupt onset of fever, sore throat, headache, abdominal pain; pharyngeal tonsillar inflammation, often (but only 50% of the time) with yellowish exudates, swollen uvula; tender anterior cervical lymph nodes; scarlatiniform rash.

B. **Viral illness is suggested by absence of fever, rhinorrhea, obstruction of the nasal passage(s), cough, conjunctivitis, hoarseness** (which have up to 80% negative predictive value), and **diarrhea.** Viral infection is especially common in children less than 3 years of age (16).

C. **Differential diagnosis.** Several experts have tried to summarize the clinical presentation of GAS versus viral infections **(Table 1.1).**

II. **Laboratory testing should be performed in patients with acute pharyngitis whose clinical and epidemiologic features suggest GAS infection.** See Sec. I.

A. **Throat culture.** For GAS infection, the accuracy of a single throat culture plated on sheep blood agar is approximately 95%. Plates that are negative at 24 hours should be reexamined at 48 hours (10).

Table 1-1. Differentiating features of pharyngitis caused by group A streptococci and viruses

	"Classic" Streptococcal Pharyngitis	Viral Pharyngitis
Season	Late winter or early spring	All seasons
Age	Peak: 5–11 yr	All ages
Symptoms	Sudden onset	Onset varies
	Sore throat, may be severe	Sore throat, often mild
	Headache	Fever varies
	Abdominal pain, nausea, vomiting	Myalgia, arthralgia
		Abdominal pain may occur with influenza A or EBV
Signs	Pharyngeal erythema and exudate	Characteristic enanthems
	Tender, enlarged anterior cervical nodes	Characteristic exanthems
	Palatal petechiae	**Often have cough, rhinitis, hoarseness, conjunctivitis, or diarrhea**
	Tonsillar hypertrophy	
	Scarlet fever rash	
	Absence of cough, rhinitis, hoarseness, conjunctivitis, and diarrhea	

Source: Modified from Tanz RR, Shulman ST. Pharyngitis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and practice of pediatric infectious diseases.* New York: Churchill/Livingstone, 1997:202.

Throat swab specimens should be obtained from the surface of both tonsils (or tonsillary fossae) and the posterior pharyngeal wall. Other areas of the oropharynx and mouth are unacceptable for sampling, and these sites should not be touched before or after the appropriate areas have been sampled (10).

Interpretation of a positive result is complicated by the fact that colonization with group A streptococci is common. Thirty percent to 35% of asymptomatic grade schoolers in the winter may be colonized with group A streptococci. If these carriers have a true superimposed viral pharyngitis, a throat culture will show GAS infection. Since the clinician does not culture for viruses, this type of patient is assumed to have GAS infection and is often treated. This is one reason those patients with a sore throat and characteristics of viral illness only (Sec. I.B) do not need to be cultured.

B. **Rapid streptococcal antigen test.** This test has excellent specificity (>95%), so a **positive test for clinical purposes establishes the diagnosis**. However, the sensitivity of the antigen test is between 80% to 90% or even lower, when compared with cultures, so a **negative antigen test should be confirmed with conventional blood agar plate culture (10,16).** An area of debate is whether those who are antigen negative and culture positive may simply be colonized. Rapid identification and treatment of GAS pharyngitis can reduce the risk of spread of GAS infection, allowing these patients to return to school, day care, or work sooner and can reduce morbidity associated with this illness (10,16). Rapid therapy is not essential to prevent acute rheumatic fever (16). See Sec. III.

C. **Antibody studies** (ASO, streptozyme) are **not advised.** This test is more helpful in confirming prior GAS infections in patients suspected of having acute rheumatic fever or acute glomerulonephritis. It is also helpful in prospective epidemiologic studies conducted to separate patients with acute infections from those who are carriers (10).

III. **Therapy. Prior studies have shown that therapy can be safely postponed up to 9 days after onset of symptoms and still prevent acute rheumatic fever (10,16).** GAS infection is usually a self-limited disease: fever and constitutional symptoms disappear spontaneously within 3 to 4 days of onset even without therapy (10), which has resulted in difficulty reaching statistical significance for penicillin therapy in small placebo-controlled studies. Therefore the clinician has considerable flexibility in initiating therapy.

A. **If the rapid antigen test is positive, treatment is indicated.** If a rapid diagnostic test is negative, treatment is based on potential risk (i.e., underlying rheumatic heart disease) and clinical suspicion until