AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

Rapid access card enclosed

The Practical Journal for Emergency Physicians

Emergency Medicine Reports™

Volume 18, Number 26

December 22, 1997

Antibiotic Update 1998: Outcome-Effective Treatment Guidelines for Bacterial Infections Managed in the Primary Care and Emergency Department Settings

Author: **Gideon Bosker, MD, FACEP,** Associate Clinical Professor, Department of Emergency Medicine, Oregon Health Sciences Center, Portland, OR. Assistant Clinical Professor, Section of Emergency Services, Yale University School of Medicine.

Peer Reviewers: **Norman C. Christopher, MD,** Director, Emergency and Trauma Services, Children's Hospital Medical Center of Akron, Akron, OH; **Stephen P. Ernst, PharmD,** Clinical Pharmacy Coordinator, Columbia Terre Haute Regional Hospital, Terre Haute, IN; **Jonathan Edlow, MD** Clinical Director, Beth Israel and Deaconess Medical Center, Boston, MA; Instructor in Medicine, Harvard Medical School, Cambridge, MA; **Albert Weihl, MD,** Emergency Medicine Residency Program Director, Yale-New Haven Medical Center, Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine.

Selecting antibiotics in the emergency department (ED) and primary care setting is a confusing, critical, and controversial exercise with formidable financial and clinical implications. Not surprisingly, with the introduction of so many new antimicrobial agents, the noise level in the "antibiotic of choice" arena has become almost deafening. There are claims and counter-claims for the superiority of one drug over another or of one class over another, with many of these opinions being rendered on the basis of personal anecdotal experience and selective interpretation of clinical trials. Because precise delineation of an etiologic agent is often impractical or unnecessary in the outpatient environment, antibiotic selection is almost always empiric and rarely benefits, at least initially, from microbiologic identification or susceptibility results.

But there are other pitfalls as well. Many patients may not require antibiotic therapy, although distinguishing among patients who do and do not require antimicrobial intervention can be a formidable clinical challenge. Even if an antibiotic with an appropriate spectrum of coverage is identified, there is always the issue of medication compliance, which can be woefully inadequate in the case of agents requiring multiple daily dose administration and prolonged courses of therapy. Aside from ensuring targeted spectrum of coverage, the issues of palatability, toleration, side effects, and convenience are fundamental to maximizing cure rates in the real-world environment.

With the recent explosive growth of the antibiotic pharmacopoeia, appreciating subtle but clinically important differences among antimicrobials has become increasingly difficult. In this regard, newer quinolones have become available that have expanded indications for community-acquired pneumonia (CAP), and one advanced generation macrolide is now indicated for parenteral therapy in hospitalized patients with lower respiratory tract infections. It may be difficult for clinicians to keep abreast of new indications, new agents, and their clinical implications. Unfortunately, the selection process is never easy, even for well-educated practitioners at the front lines of clinical practice. Experienced clinicians, especially those who work in a managed care environment, are particularly aware of the debate: To choose a new, more conveniently dosed and, usually, more costly, antimicrobial with documented patient-friendliness and more predictable coverage or to choose a less expensive, vintage, warhorse drug with undesirable side effects—one that is "report card" and formulary-friendly—and which requires a 30-dose course of

EDITOR IN CHIEF
Gideon Bosker, MD, FACEP
Special Clinical Projects and Medical Education Resources
Assistant Clinical Professor
Section of Emergency Services
Yale University School of Medicine
Associate Clinical Professor
Oregon Health Sciences University

MANAGING EDITOR
David Davenport

ASSISTANT MANAGING EDITOR
Catherine Harris

EDITORIAL BOARD
Paul S. Auerbach, MD, MS, FACEP
Chief Operating Officer
Sterling Healthcare Group, Inc.
Coral Gables, Florida

Brooks F. Bock, MD, FACEP
Professor and Chairman
Department of Emergency Medicine
Detroit Receiving Hospital
Wayne State University
Detroit, Michigan

Michael L. Coates, MD, MS
Professor of Family Medicine
University of Virginia
School of Medicine

Stephen Anthony Colucciello, MD, FACEP
Assistant Clinical Professor of Emergency Medicine
University of North Carolina Medical School, Chapel Hill, North Carolina
Director, Clinical Services
Trauma Coordinator
Dept. of Emergency Medicine
Carolinas Medical Center
Charlotte, North Carolina

Alasdair K.T. Conn, MD
Chief of Emergency Services
Massachusetts General Hospital
Boston, Massachusetts

Jeffrey S. Jones, MD, FACEP
Assistant Professor and Research Director
Department of Emergency Medicine
Butterworth Hospital
Michigan State University College of Medicine
Grand Rapids, Michigan

Frederic H. Kauffman, MD, FACEP
Associate Professor of Medicine
Temple University School of Medicine
Director of Emergency Medicine Services
Temple University Hospital
Philadelphia, Pennsylvania

Larry B. Mellick, MD, MS, FAAP, FACEP
Professor and Chair
Department of Emergency Medicine
Director of Pediatric Emergency Medicine
Medical College of Georgia
Augusta, Georgia

Paul E. Pepe, MD, MPH, FACEP, FCCM
Professor and Chairman
Department of Emergency Medicine
Allegheny University of the Health Sciences
Allegheny Campus
Pittsburgh, Pennsylvania
Director, Emergency Services
Allegheny General Hospital
Pittsburgh, Pennsylvania

Norman E. Peterson, MD
Chief
Division of Urology
Denver General Hospital
Denver, Colorado

Robert Powers, MD, FACP, FACEP
Chief, Emergency Medicine
University of Connecticut
School of Medicine
Farmington, Connecticut

Steven G. Rothrock, MD, FACEP
Department of Emergency Medicine
Orlando Regional Medical Center & Arnold Palmer's Hospital for Women and Children
Orlando, Florida
Clinical Assistant Professor, Division of Emergency Medicine
University of Florida College of Medicine
Gainesville, Florida

Barry H. Rumack, MD
Director, Emeritus
Rocky Mountain Poison and Drug Center
Clinical Professor of Pediatrics
University of Colorado
Health Sciences Center
Denver, Colorado

Richard Salluzzo, MD, FACEP
Professor and Chairman of Emergency Medicine
Albany Medical College
Albany, New York

Sandra M. Schneider, MD
Professor and Chair
Department of Emergency Medicine
University of Rochester School of Medicine
Rochester, New York

John A. Schriver, MD
Chief, Section of Emergency Medicine
Yale University School of Medicine
New Haven, Connecticut

David Sklar, MD, FACEP
Professor and Chair
Department of Emergency Medicine
University of New Mexico School of Medicine
Albuquerque, New Mexico

Corey M. Slovis, MD, FACP, FACEP
Professor and Chairman
Department of Emergency Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

J. Stephan Stapczynski, MD
Associate Professor and Chairman
Department of Emergency Medicine
University of Kentucky Medical Center
Lexington, Kentucky

Charles E. Stewart, MD, FACEP
Associate Professor
in Emergency Medicine
University of Rochester School of Medicine
Rochester, New York

David A. Talan, MD, FACEP
Chairman and Associate Professor of Medicine
UCLA School of Medicine
Department of Emergency Medicine
Olive View/UCLA Medical Center
Los Angeles, California

Albert C. Weihl, MD
Program Director
Emergency Medicine Residency
Assistant Professor of Medicine and Surgery
Department of Surgery
Section of Emergency Medicine
Yale University School of Medicine

Allan B. Wolfson, MD, FACEP, FACP
Program Director,
Affiliated Residency in Emergency Medicine
Professor of Emergency Medicine and Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

© 1997 American Health Consultants
All rights reserved

therapy. That is the question.

The fact is, no matter how we frame the issue, nothing seems to produce more debate among health care practitioners than selection strategies for outpatient antibiotic therapy. In addition, it should be stressed that in clinical environments that are patient volume-driven and that are dominated by capitated reimbursement arrangements, there are powerful incentives to "cure" infections the first time around (i.e., within the framework of the first prescription generated in the initial visit).

Although optimizing cure rates with so-called convenient, dose- and duration-friendly branded agents that provide appropriate coverage may be perceived as costly on a course of therapy basis, it is important to stress that antimicrobials with these properties can also help avoid the unnecessary costs of patient re-evaluations, return visits, treatment failures, patient dissatisfaction, and the pharmacological reservicing cost associated with initiating a second course of antibiotics. In this sense, antibiotics that lower barriers to clinical cure can be seen as "productivity" tools that improve efficiency of clinical care and, potentially, reduce the overall costs associated with outpatient management of infections.

Clearly, coverage of implicated pathogens is critical for cost-effective care. Making matters worse is the difficulty of identifying an appropriate, cost-effective antibiotic that is "smart" enough to provide coverage against the most likely offending organisms in a particular patient. For example, in children with otitis media, a so-called "high-performing" antibiotic must be "smart" enough to cover appropriate species of Streptococcus pneumoniae, Haemophilus influenzae, and M. catarrhalis. In adults with CAP, the corral of coverage must be expanded to include atypical organisms—Mycoplasma pneumoniae, Legionella pneumophila, and Chlamydia pneumoniae—which are now implicated in about 22% of cases with CAP.

In the real world, the road from the clinician's prescription pad to clinical cure depends on a constellation of factors (i.e., beyond spectrum of coverage) including prescription, patient, drug, and in the case of suspensions, parent-resistance (PPD factors). The PPD approach to antimicrobial selection in the emergency and primary care setting attempts to account for all the factors—and potential barriers—that go into the equation for clinical cure. These include cost of the medication, compliance profile, palatability issues, duration of therapy, gastrointestinal side-effect profile, convenience of dosing, and spectrum of coverage.

Overcoming these barriers to clinical cure is essential for enhancing clinical outcomes and reducing the costs of therapy and complications of the disease. The goal, of course, is to identify an antibiotic that will simultaneously manage cost, manage coverage, and manage compliance, so that, ultimately, the clinician can manage care of the patient in an outcome-effective manner.

Finally, bacterial infections are commonly encountered in the ED and urgent care setting, and emergency physicians are among the major prescribers of antibiotics. Although emergency physicians mainly prescribe oral antibiotics, parenteral antibiotics are also used to initiate therapy for hospitalized patients, who will then continue oral treatment in the outpatient setting following discharge. An understanding of how initial selection of intravenous antibiotic therapy in the ED or hospital may affect subsequent choices for completing the treatment course with oral agents has become an important cost and clinical consideration for the emergency and primary care practitioner.

With these issues in mind, this 1998 Antibiotic Update article, which presents a thorough discussion of recent advances, new indications, intravenous/oral treatment combinations, and controversies, outlines a rational, systematic approach to antimicrobial selection in the ED and primary care setting, with a special emphasis on indications and rational guidelines for day-to-day use.

—The Editor

The Antimicrobial Armamentarium: Uses and Abuses

In addition to the older, so-called "standard" antibiotics—most notable among them, the penicillins and sulfa drugs—there are many newer oral agents, particularly cephalosporins, quinolones, and macrolides, that play a role in treating bacterial infections commonly encountered in the ED and primary care setting. Typically, antibiotics have been evaluated by comparing spectrum of activity, clinical efficacy, toxicity (adverse drug

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Senior Vice President/Group Publisher: David Wilson
Managing Editor: David Davenport
Asst. Managing Editor: Catherine Harris
Marketing Manager: Deb Zelnio

GST Registration No.: R128870672

Periodical postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to ***Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Copyright © 1997 by American Health Consultants, Atlanta, GA. All rights reserved. Reproduction, distribution, or translation without express written permission is strictly prohibited.

Back issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $87 each; 10 or more additional copies, $58 each.

Accreditation

Emergency Medicine Reports'™ continuing education materials are sponsored and supervised by American Health Consultants. American Health Consultants designates this continuing education activity as meeting the criteria for 50 credit hours in Category 1 for Education Materials for the Physician's Recognition Award of the American Medical Association, provided it has been completed according to instructions.

This CME activity was planned and produced in accordance with the ACCME Essentials. ***Emergency Medicine Reports*** also is approved by the American College of Emergency Physicians for 52 hours of ACEP Category 1 credit and has been approved for 50 Category 2B credit hours by the American Osteopathic Association. This program has been reviewed and is acceptable for up to 50 Prescribed credit hours by the American Academy of Family Physicians. Term of approval is for one year from beginning distribution date of 1/97 with option to request yearly renewal.

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail: custserv@ahcpub.com
Editorial E-Mail: david_davenport@medec.com
World Wide Web page: http://www.ahcpub.com

Subscription Prices

1 year *with* 52 ACEP/AMA/50 AAFP Category 1/Prescribed credits (50 AOA Category 2B credits): $387
1 year *without* credit: $287

2 years *with* 104 ACEP/AMA/100 AAFP Category 1/Prescribed credits (100 AOA Category 2B credits):$814
2 years *without* credit:$574

3 years *with* 156 ACEP/AMA/150 AAFP Category 1/Prescribed credits (150 AOA Category 2B credits): $1221
3 years *without* credit: $861
Resident's' rate $143.50

All prices U.S. only.
U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

Questions & Comments

Please call **David Wilson,** Publisher, at (404) 262-5430, or **David Davenport,** Managing Editor, at (404) 262-5475 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Bosker is on the speaker's bureau of Parke-Davis and Pfizer pharmaceutical companies.

reactions and interactions), pharmacokinetics (convenience and compliance with dosing), and cost. In addition to these parameters, there are at least two additional factors that must be taken into account when comparing antibiotics: 1) the selective pressure for the emergence of resistant organisms; and 2) the overall cost-effectiveness or outcome cost.

The newer antibiotics, although possessing variable increases in the spectrum of activity over older agents, have uniformly been shown in clinical trials to be equally, but rarely more efficacious, than standard therapy. It should be stressed, however, that within the context of clinical trials, patients are frequently given incentives through counseling and pill counts to comply with their regimens. Notably, outcomes in these studies may deviate from those seen in the "real world," where noncompliance with antibiotics is a major barrier to clinical cure. Consequently, it may be difficult to extrapolate from cure rates published in idealized clinical trials to the front lines of emergency medicine practice.

Generally speaking, most advantages associated with newer drugs are typically found in parameters other than spectrum of coverage. For example, some of the newer agents have a significantly improved toxicity or drug interaction profile compared with conventional therapy. One drawback of newer agents—even those that belong to familiar classes of antibiotics—is limited information regarding specific toxicity issues. In this regard, temafloxacin, a fluoroquinolone antibiotic, was withdrawn from the worldwide market just four months after approval in the United States because of subsequent reports of serious hemolysis, with or without other organ system dysfunction. This adverse reaction (temafloxacin syndrome) was not recognized in patients participating in the clinical trials, but became evident when nearly 200,000 prescriptions were written after approval.[1,2]

Outcome Considerations in Antibiotic Selection

Barriers To Clinical Cure for Oral Antibiotic Therapy. In the best and most cost-effective of all worlds, the antibiotic selection process for common infections such as pneumonia, acute otitis media, cystitis, and PID would be based on an outcome-oriented assessment of the total cost of cure associated with managing these conditions. This review will underscore the importance of identifying therapeutic agents that, because of favorable cost, compliance, safety, and pathogen coverage features, are able to reduce barriers to clinical cure. In general, antimicrobial agents that satisfy these criteria will improve "first time around" cure rates and thereby reduce overall outcome costs.

Among the factors that would be included in an outcome analysis (i.e., the total costs associated with diagnosis, management, and cure of outpatient infection) are the following: cost of the medication(s) used for the initial course of antibiotic therapy; cost of the initial physician visit; human resource time (telephone time, revisits, etc.) required to service queries regarding the drug and/or its side effects; the cost of practitioner re-evaluations for treatment failures; hospitalization costs due to treatment failure; the cost of additional courses of therapy to achieve therapeutic endpoints (clinical improvement or bacterial eradication); the economic opportunity cost sustained by patients (or parents) because of time lost from work to care for themselves or their child; the cost of medications or other devices (diapers, etc.) to service the gastrointestinal side effects (diarrhea) of the medications; and the short- and long-term sequelae of treatment failures or repeated episodes of infection.

Although comprehensive, outcome-directed studies addressing all of these variables for most outpatient infections are not currently available, other outcome-sensitive drug therapy assessment tools can be pressed into service for the purpose of drug selection. In this regard, the prescription, patient, and drug resistance (PPD) approach to drug selection permits emergency physicians to evaluate and compare the clinical success profiles of one antibiotic vs. another. These comparisons are based on a synthetic approach constructed according to established specifications and parameters such as price, daily dose frequency, duration of therapy, palatability, side-effect profile, and spectrum of coverage. [3-15]

From the perspective of prescribing antibiotics in the outpatient setting, it must be emphasized that each of the PPD resistance barriers is important, and that if one or more of these barriers (cost, side-effect profile, lack of convenience, inadequate coverage of pathogens) is of sufficient magnitude, it may influence the overall real-world cure rate.[9,11,14,16] These barriers are discussed in the following sections.

Prescription Resistance, Patient Resistance, and Drug Resistance (PPD System)

PPD Resistance Barriers for Oral Antibiotic Therapy. The prescription, patient, and drug (PPD) resistance approach to drug selection permits primary care and emergency physicians to evaluate and compare the clinical success profiles of one antibiotic vs. another according to established specifications and parameters, such as price, daily dose frequency, duration of therapy, side-effect profile, and spectrum of coverage.[3-5]

In this regard, having a patient achieve a favorable outcome requires negotiating several real-world PPD resistance barriers. Using this outcome-based, cost-effectiveness-oriented, "real-world" approach, some antibiotics will fare better than others. From the perspective of prescribing antibiotics in the ED, it must be stressed that each of these three resistance barriers is equally important in determining whether clinical cure is likely. These barriers are discussed in the following sections.

Prescription Resistance. Prescription resistance refers to the likelihood that patients will actually *fill* their prescription. Studies show that up to 25% of patients given a prescription for an antibiotic never even fill their prescription, and the risk of non-filling increases with the cost of the medication.[3,5] Accordingly, the primary determinant of prescription resistance is the cost of the medication.

In addition to the cost of the antibiotic, other factors affecting the patient's propensity for filling the prescription include: 1) The clinical provider's persuasiveness in convincing the patient he or she needs the antibiotic as part of their therapeutic program; 2) "word of mouth" about the drug (i.e., is it perceived by the community as a tolerable, or poorly tolerated, medication?); 3) previous experiences with the medication; and 4) the patient's perception of the seriousness of his or her condition.

When the cost of a course of therapy is high, if the ED physician has not taken the time to persuade the patient of the importance of filling his or her prescription, or the patient perceives

his or her illness as mild, the prescription resistance barrier is high and, therefore, will affect clinical outcomes.

Patient Resistance. Patient resistance refers to the likelihood that the patient will actually *take* the medication for the entire course of therapy, assuming, of course, that the prescription-resistance barrier was low enough to induce the patient to actually fill the prescription. Once filled, however, there are a number of factors that determine whether patient resistance will be high or low—or, put differently, how likely the patient is to be compliant with his or her medication.

The principal factors determining patient resistance are the daily dose frequency of the medication, the duration of therapy, the side-effect profile, and the discontinuation rate of the drug. Not surprisingly, the antibiotic with the lowest patient resistance profile would be characterized by a well-tolerated, single-dose therapy administered under supervision. Examples of low patient resistance regimens include a single 2 g dose of metronidazole for trichomoniasis, single-dose therapy for gonorrhea, a single 1 g dose of azithromycin for uncomplicated chlamydial cervicitis, or a single 150 mg dose of fluconazole for the treatment of candida vaginitis.

These approaches satisfy the criteria for Universal Compliance Precautions (UCP) because, in general, administration of single-dose therapy especially when given under supervision prevents noncompliance-mediated therapeutic failures from undermining the success of a drug regimen. Generally speaking, patient resistance is acceptable, but still less than perfect, for therapeutic courses based on antibiotics dosed on a once-daily basis and given for five or fewer days, and that have a low incidence of side effects (usually gastrointestinal in origin). Patient resistance becomes an important barrier to clinical cure for medications given on a bid or greater daily dose frequency, those given for seven days or more, and for agents that have gastrointestinal side effects that are severe enough to produce drug discontinuation.[4,5]

Special considerations apply to antibiotic suspensions for the pediatric age group. Because children do not self-administer medications, compliance in the pediatric age group depends, to a great extent, upon the parent's willingness and motivation to give the antibiotic. Similarly, medications that require refrigeration, must be administered by day care or school personnel, or require special timing requirements with respect to food intake, increase parent resistance and, therefore, may compromise proper, timely administration.[16,17] In particular, drugs with gastrointestinal side effects—especially diarrhea—create a "clean-up" factor that may discourage parents from completing the entire course of therapy as prescribed. This can be called "parent" resistance. In this regard, at least one study has shown that poor medication compliance is the most common cause of antibiotic treatment failures.[17]

The effect of patient resistance (i.e., compliance profile) barriers on clinical outcomes in outpatient infections should never be underestimated. Even when the cost of the medication is sufficiently low to encourage prescription fulfillment, if patient resistance factors are sufficiently imposing, clinical cure rates will be compromised.

Drug Resistance. Drug resistance refers to the spectrum of coverage (i.e., antimicrobial activity) provided by the antibiotic against the most likely organisms encountered in the specific infection against which the drug is directed. For example, organisms targeted for empiric therapy in community-acquired respiratory infections include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Moraxella catarrhalis*. *Chlamydia pneumoniae* is also cited as an increasingly common etiologic agent.

An antibiotic with proven activity against all these organisms would provide optimal coverage and, therefore, would be associated with a low drug-resistance barrier. On the other hand, an antibiotic with activity against only three (or fewer) of these organisms might produce therapeutic failures in a significant percentage of cases and, therefore, would be associated with a drug-resistance barrier obstructing the outcome highway. The risk of infection caused by specific organisms is often related to patient characteristics. *H. influenzae* is unusual in nonsmoking patients without COPD, and *M. pneumoniae* is less frequent outside the youngest adult age group.

Naturally, drug resistance must always be considered when selecting an antibiotic. Even when the medication is inexpensive and well-tolerated (i.e., prescription- and patient-resistance barriers are low), if the drug fails to provide optimal activity at the "business end" (it has poor spectrum of coverage against anticipated organisms at the site of infection), cure rates will be compromised.

Optimal PPD Profiles. Optimal PPD profiles are characterized by antibiotics with low prescription, patient, and drug resistance. In this regard, the most desirable agent—in other words, the antibiotic producing the greatest likelihood of clinical success in the real-world patient encounter—is inexpensive enough to encourage prescription filling, well-tolerated enough by the patient to promote compliance, and active against all the anticipated pathogens so that its empiric use will provide appropriate coverage without the necessity for retreatment due to resistance organisms.

Recent Advances in Antibiotic Therapy: New Agents, Formulations, Treatment indications, and Antimicrobial Combinations

Overview and General Principles. Among the most important advantages of the newer antibiotics is improved pharmacokinetics, which permits less frequent dosing, increased convenience, shorter duration of therapy, and increased compliance. Azithromycin is one important example of a newer agent with these features. In general, compliance is thought to be enhanced by once- or twice-daily dosing compared to more frequent administration.[3,4] Although this has been confirmed by "science of compliance" studies, other factors such as a good doctor-patient relationship reinforcing the importance of taking medications as prescribed may also be important in generating improved compliance.[5]

As a rule, the advantage of less-frequent dosing must always be weighed against the generally higher cost of newer antibiotics as well as the antibiotic's spectrum of activity. In this regard, although newer antibiotics are generally more expensive compared to established agents, there is considerable variability among the newer agents. *(See Table 1.)*

Furthermore, the appropriateness of broad-spectrum antibiotic therapy in a setting in which narrower-spectrum therapy would suffice must be questioned, especially because of the selective

Table 1. Commonly Used Outpatient Antibiotics

Antibiotic	Brand Name	Usual Adult Dose*	Cost†
CEPHALOSPORINS			
First Generation:			
Cephalexin		250, 500 mg qid	$20, $39
Cefadroxil	Duricef	500, 1000 mg bid	$62, $116
Second Generation:			
Cefuroxime axetil	Ceftin	250, 500 mg bid	$63, $122
Cefprozil	Cefzil	250, 500 mg bid	$55, $107
Cefaclor	Ceclor	250, 500 mg tid	$56, $110
Loracarbef‡	Lorabid	200, 400 mg bid	$60, $76
Third Generation:			
Cefixime	Suprax	200, 400 mg qd	$31, $61
Cefpodoxime proxetil	Vantin	200, 400 mg bid	$63, $126
PENICILLINS			
Benzathine penicillin G		1.2 MU IM	$11
Penicillin V		250, 500 mg qid	$2, $4
Amoxicillin	Amoxil	250, 500 mg tid	$5, $10
Dicloxacillin		250, 500 mg qid	$15, $26
Amoxicillin-clavulanate	Augmentin	250, 875 mg bid	$57, $80
FLUOROQUINOLONES			
Ciprofloxacin	Cipro	250, 500, 750 mg bid	$54, $62, $110
Ofloxacin	Floxin	200, 300, 400 mg bid	$59, $70, $73
Norfloxacin	Noroxin	400 mg bid	$51
Lomefloxacin	Maxaquin	400 mg qd	$64
Enoxacin	Penetrex	200, 400 mg bid	$63, $63
Levofloxacin	Levaquin	500 mg qd × 7-14 days	$78
Sparfloxacin	Zagam	400 mg day 1, 200 mg days 2-10	$76
MACROLIDES			
Erythromycin		250, 500 mg qid	$6, $10
Clarithromycin	Biaxin	250, 500 mg bid	$63, $63
Azithromycin	Zithromax	500 mg day 1, 250 mg days 2-5	$36ψ
MISCELLANEOUS			
Trimethoprim-sulfamethoxazole	Septa, Bactrim	1 double-strength bid	$4
Doxycycline	Vibramycin	100 mg bid	$4
Clindamycin	Cleocin	150, 300 mg qid	$36, $88
Metronidazole	Flagyl	500 mg tid	$7
Fosfomycin	Monurol	3 g (one dose)	$22

* Oral unless otherwise stated

† Average wholesale price (AWP) for 10 days of therapy unless otherwise stated (*1997 Red Book.* Montvale, NJ: Medical Economics Data Production Co; 1997). The cost represents the average cost of generic formulations when brand name is not listed.

‡ A carbacephem antibiotic (see text)

ψ Five days of therapy constitutes an entire course of therapy

pressure for resistance exerted. There are currently numerous examples of resistant organisms in both the community and hospital settings, including methicillin-resistant staphylococci, VISA, VRE, penicillin- and cephalosporin-resistant pneumococci, penicillin- and tetracycline-resistant gonococci, Beta-lactamase-producing *H. influenzae* associated with amoxicillin resistance, and multiple antibiotic-resistant gram-negative bacilli.[6,7,18]

It appears that the increasing incidence of antibiotic resistance is in large part due to antibiotic prescribing and misuse.[19] Despite increased worry over antibiotic resistance, physicians are prescribing more expensive, broad-spectrum antibiotics (especially cephalosporins and quinolones) in the United States.[20] Because of uncertain benefits, there has recently been a plea to decrease inappropriate antibiotic use, especially in patients with acute bronchitis who do not have associated chronic obstructive pulmonary disease (COPD).[21] Patients with acute bronchitis that is unrelated to COPD probably do not benefit from antibiotic therapy. It should be stressed, however, that in patients with COPD, antibiotics do appear to have a role in the treatment of exacerbations caused by bacterial bronchitis.[22]

Although the newer antibiotics have a wide variety of approved indications *(See Table 2)*, these agents should be used more judiciously in patients in whom bacterial resistance, allergy, intolerance, or a significant opportunity to simplify therapy exists. Although it is often said that 5-10% of penicillin-allergic patients will have a reaction to cephalosporins, the true inci-

Table 2. Approved Indications for Newer Oral Antibiotics*

ANTIBIOTIC	UPPER RESPIRATORY TRACT			LOWER RESPIRATORY TRACT		GENITOURINARY TRACT/ SEXUALLY TRANSMITTED DISEASES					MISCELLANEOUS		
	Pharyngitis/ Tonsillitis	Otitis Media	Sinusitis	ABECB	CAP	Uncomp UTI	Comp UTI	Prostatitis	Uncomp GC	Uncomp NGU/C	USSSI	B&J	Infectious Diarrhea
Cefuroxime axetil	✔	✔	✔	✔	✔	✔			✔		✔		
Cefprozil	✔	✔	✔	✔							✔		
Cefaclor	✔	✔		✔	✔	✔	✔				✔		
Loracarbef	✔	✔	✔	✔	✔	✔	✔				✔		
Cefixime	✔	✔		✔		✔			✔				
Cefpodoxime proxetil	✔	✔		✔	✔	✔			✔		✔		
Amoxicillin/ clavulanate		✔	✔	✔	✔	✔	✔						
Ciprofloxacin			✔	✔	✔	✔	✔				✔	✔	✔
Ofloxacin				✔	✔	✔	✔	✔	✔	✔	✔		
Norfloxacin						✔	✔		✔				
Lomefloxacin				✔†		✔	✔						
Enoxacin						✔	✔		✔				
Levafloxacin			✔	✔	✔	✔	✔				✔		
Sparfloxacin				✔	✔								
Fosfomycin						✔							
Clarithromycin	✔	✔	✔	✔	✔						✔		
Azithromycin	✔	✔		✔	✔				✔	✔	✔		

* *1997 Physicians' Desk Reference*. Montvale, NJ: Medical Economics Data Production Co; 1997.
† Not *S. pneumoniae*

ABECB = Acute bacterial exacerbation of chronic bronchitis; CAP = Community-acquired pneumonia; Uncomp UTI = Uncomplicated urinary tract infection; Comp UTI = Complicated urinary tract infection; Uncomp GC = Uncomplicated gonorrhea; Uncomp NGU/C = Uncomplicated nongonococcal urethritis/cervicitis; USSSI = Uncomplicated skin and skin structure infection; B&J = Bone and joint infection

dence appears to be much less (about 1-2%).[23] Consequently, cephalosporins may safely be given to the majority of patients with a history of penicillin allergy; however, avoid such therapy in the case of a potential IgE-mediated allergy (anaphylaxis, urticaria).[24]

Cephalosporins. The extended-spectrum cephalosporins include the designated "second-generation" agents cefuroxime axetil and cefprozil.[25,26] The carbacephem antibiotic, loracarbef, has a spectrum of activity similar to these agents.[27] A minor modification of the cephalosporin ring of cefaclor results in the carbacephem designation. These antibiotics have good activity against common gram-positive organisms except for methicillin-resistant staphylococci and enterococci. They are reliably active against *H. influenzae*, *M. catarrhalis*, and many strains of *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. *(See Table 2.)*

In general, these agents offer no significant advantage over trimethoprim-sulfamethoxazole (TMP-SMX) for upper or lower respiratory tract pathogens, with the exception of *Streptococcus pyogenes*, which can cause pharyngitis or tonsillitis. Penicillin remains the drug of choice for pharyngitis, except in cases in which a high risk of noncompliance can be anticipated, in which case a macrolide with shorter duration of therapy should be considered. Skin and skin structure infections generally respond well to a first-generation cephalosporin or a penicillinase-resistant penicillin such as dicloxacillin. Cefuroxime axetil has been shown to be as effective as doxycycline in early Lyme disease.[28]

The "third-generation" cephalosporins include cefixime and cefpodoxime proxetil.[29,30] These antibiotics are characterized by an extended spectrum against gram-negative organisms such as *E. coli* and Klebsiella; nosocomial bacteria such as *Pseudomonas aeruginosa*, Enterobacter, Serratia, and others are generally resistant to these agents. Cefpodoxime proxetil has moderate gram-positive activity, while that of cefixime is poor.

These antibiotics have a variety of approved indications but are generally not superior to established agents for the same indications. *(See Table 2.)* Cefpodoxime proxetil has a lower cure rate for uncomplicated urinary tract infections than comparable agents.[31] Both of these agents are effective as one dose-therapy for uncomplicated gonorrhea.[32,33]

Penicillins. Although no dramatic advances have been reported in the penicillin-related antibiotics, the most important recent "modifications" among antimicrobials in this category has been the the new dosing schedule approved for amoxicillin-clavulanate in the treatment of otitis media. In this regard, recent approval for BID administration of this antibiotic should be noted, although this agent does not share the full compliance-promoting benefits of once-daily administration seen with other agents such as azithromycin, cefixime, and cefpodoxime. Although palatability of the amoxicillin is quite acceptable, the incidence of diarrhea is reported in large studies to be about 16%.[30] In vitro coverage of most bacterial offenders causing acute otitis media is favorable.

Amoxicillin-clavulanate. From a practical perspective, amoxicillin-clavulanate is now made in a 200 mg/5 mL and 400 mg/5 mL suspension. This new suspension has a lower concentration of clavulanate and thus has fewer GI side effects (especially diarrhea). Furthermore, dosing differs for these two new suspensions. Otitis media should be treated with 45 mg/kg bid, a more convenient dosing pattern than the previous tid recommendations, if these suspensions are used. Finally, the new suspensions contain aspartame and should not be used by phenylketonurics.

Quinolones. The currently available quinolones include levofloxacin, sparfloxacin, ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, and enoxacin.[34-37] *(See Table 2.)* Prior to the recent introduction of the extended spectrum quinolones, levofloxacin and sparfloxacin, these antibiotics were characterized by extensive activity against gram-negative organisms including *H. influenzae*, *M. catarrhalis*, and most enteric bacilli. In addition, ciprofloxacin has good activity against *P. aeruginosa*. Although the quinolones have no useful anaerobic activity, they have moderate gram-positive activity, but resistance has emerged quickly in *S. aureus* and streptococcal activity is borderline, except in the case of the newer quinolones levofloxacin and sparfloxacin (see below). There have been breakthrough bacteremias caused by *S. pneumoniae* reported on ciprofloxacin.[38,39] The quinolones have excellent activity against bacteria commonly causing diarrheal illnesses, including *E. coli*, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*. This class of drugs is contraindicated in pregnancy and in children less than 18 years of age.

Levofloxacin. From an emergency medicine and primary care perspective, one of the most important developments has been the introduction of the extended spectrum quinolones. In this regard, levofloxacin, the S-enatiomer of ofloxacin, is a new fluoroquinolone antibiotic recently approved by the FDA. It is an extended spectrum quinolone that, compared with older quinolones, has improved activity against gram-positive organisms including *Streptococcus pneumoniae*. This has important drug selection implications for management of patients with community-acquired pneumonia and exacerbations of COPD. The active stereoisomer of ofloxacin, levofloxacin is available in a parenteral preparation or as a once daily oral preparation that is given for 7-14 days.

Levofloxacin is indicated for the treatment of adults (> 18 years of age) with mild, moderate, and severe infections including acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, and complicated urinary tract infections including acute pyelonephritis.[40] This antimicrobial is active against many gram-positive organisms including *S. pneumoniae*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *S. pyogenes*, and it also covers atypical pathogens including *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*. It is also active against gram-negative organisms including *Enterobacter cloacae*, *E. coli*, *H. influenza*, *H. parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

When given orally, levofloxacin is dosed once daily, is well absorbed orally, and penetrates well into lung tissue.[40] It is active against a wide range of respiratory pathogens including atypical pathogens and *S. pneumoniae* resistant to penicillin.[37,38] In general, levofloxacin has similar activity against gram-positive organism as ofloxacin and ciprofloxacin, and it is more active than ofloxacin and slightly less active than ciprofloxacin against gram-negative organisms.[41,42] In particular, it should be noted that levofloxacin is less active against *Pseudomonas aeruginosa* than ciprofloxacin.[41,42] Reflecting this sensitivity data, levofloxacin is FDA approved for treating pseudomonal infections of the urinary tract only. In contrast, it has been reported to be more active than the older quinolones against *S. pneumoniae* resistant to penicillin.[43] The drug is available as both an oral and parenteral form, and the oral and IV routes are interchangeable (i.e., same dose). Levofloxacin is generally well tolerated (incidence of adverse reactions, <7%).

Levofloxacin is supplied in a parenteral form for IV use and in 250 mg and 500 mg tablets. The recommended dose is 500 mg IV or orally qd for 7-14 days for upper or lower respiratory tract infections and uncomplicated skin and skin structure infections, and 250 mg qd for 10 days for complicated UTI or acute pyelonephritis. Food does not affect the absorption of the drug, but it should be taken at least two hours before or two hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparation with zinc. Dosage adjustment is recommended in patients with impaired renal function (clearance < 50 mL/min).[40] The drug is well-tolerated, with the most common side effects including nausea, diarrhea, headache, and constipation.[40] All quinolones have been associated with cartilage damage in animal studies, and therefore, they are not recommended for use in children, adolescents, pregnant and nursing women.

Comparative trials (generally available in abstract form) suggest that levofloxacin is as effective as cefuroxime axetil, cefaclor, and amoxicillin/clavulanate in upper or lower respiratory infections.[44-46] In patients with community-acquired pneumonia, IV levofloxacin with step-down to oral therapy was superior to ceftriaxone with step-down therapy to cefuroxime axetil.[47] About 22% of patients in the cephalosporin arm required the addition of erythromycin or doxycycline due to the presence of atypical respiratory pathogens. The clinical response rates (cure plus improvement) were 88-97% for levofloxacin. Microbiolog-

ical eradication was reported to be 94-98%; however, a large number of patients (32-43%) were not evaluable for this end point.[44,46,47]

Levofloxacin, ofloxacin, and another recently approved drug, sparfloxacin, are the only quinolones approved by the FDA for respiratory tract infections, in particular for empiric therapy for community acquired pneumonia. Currently, such macrolides as azithromycin or clarithromycin are recommended for pneumonia in ambulatory, otherwise healthy adults. For older patients, an oral cephalosporin such as cefuroxime axetil—with or without the addition of a macrolide to provide coverage of atypical pathogens—may be considered.[43] In this patient subgroup, levofloxacin provides an effective, safe, and cost-attractive outpatient alternative to two-drug combinations, especially in the elderly patient who is deemed well enough to be treated out of hospital and in whom coverage of gram-negative organisms in addition to coverage of *Streptococcus pneumoniae* and atypical pathogens are desirable. (Please refer to "Community-Acquired Pneumonia" section below for a more detailed analysis of drug options in CAP).

Sparfloxacin. The second of two extended-spectrum fluoroquinolone antibacterial agents recently approved by the FDA, sparfloxacin was developed in Japan and is a chemically unique quinolone, with an amino substituent in the five-position and a fluorine substituent in the eight-position of the quinolone nucleus. The amino substituent enhances gram-positive activity,[48] while the fluorine substituent increases plasma half-life[49] but also appears to increase the risk of phototoxicity (e.g., lomefloxacin).

Like levofloxacin, sparfloxacin is dosed once a day and provides a wide range of coverage including activity against common gram-positive and gram-negative respiratory pathogens, as well as against the atypical pathogens *Chlamydia pneumonia* and *Mycoplasma pneumonia*. Importantly, sparfloxacin shows excellent activity against penicillin-resistant pneumococcus and multidrug-resistant *H. influenzae* and *M. catarrhalis*.

Sparfloxacin is indicated for the treatment of adults (> 18 years old) with the following infections caused by susceptible strains of the designated microorganisms: Community-acquired pneumonia (CAP) caused by *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae*, and; acute bacterial exacerbation of chronic bronchitis caused by *Chlamydia pneumoniae*, *Enterobacter cloacae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Streptococcus pneumoniae*.[49] In comparative trials, sparfloxacin was as effective as amoxicillin/clavulanate, cefaclor, erythromycin, amoxicillin, ofloxacin, or amoxicillin plus ofloxacin for clearing community-acquired pneumonia.[48,49,50-52] Sparfloxacin is more active than ciprofloxacin against *Mycobacterium tuberculosis*, but is less active against *P. aeruginosa* than ciprofloxacin with a median MIC90 two- to four-fold higher.[48]

Given this drug's excellent and appropriate spectrum of coverage for CAP and bacterial exacerbations of COPD, one issue that will clearly play a determining role in the acceptance of sparfloxacin among emergency medicine and primary care practitioners is the reported incidence of photosensitivity reactions, which, in selected individuals (i.e., active, young, outdoor-oriented individuals who are not ill enough from their CAP to require bedrest indoors) can affect patient satisfaction, and potentially, be problematic.

To gain an accurate, balanced assessment of the photosensitivity dimension of this new antimicrobial, it is important to look at the rate of photosensitivity reactions in detail and their frequency in specific patient subgroups. First, it should be stressed that photosensitivity reactions were the most common adverse reaction observed, with an overall rate of 7.9% reported among patients enrolled in all clinical trials (126 of 1585) for the drug. *Moderate to severe* phototoxic reactions occurred in 3.9% of patients. It should be stressed, however, that these adverse event rates were generated from initial trial data that included a wide variety of active, minimally ill, younger individuals with infections such as UTI and sinusitis, (two indications for which the drug is not FDA-approved or being marketed) that were not severe enough to prevent participation in normal daily activities, including outdoor exposure to sun or ultraviolet (UV). However, in patients with community-acquired pneumonia—a subgroup which, because of the morbidity and debilitation associated with this condition, is less likely to encounter sun or UV light exposure during their treatment course—the incidence of photosensitivity reaction diminished by almost 50%, to 4.1%. Moreover, there were no severe (i.e., blister-forming reactions) in CAP group, and the discontinuation rate from photosensitivity problems was only about 1%.[49]

Based on these findings, it appears as if patient selection can play a pivotal role in identifying clinical situations that will maximize the benefits of sparfloxacin, while reducing the potential side effects. In this regard, homebound patients and individuals who are not active in outdoor activities, are the most suitable candidates. All patients must be instructed to avoid exposure to the sun, bright natural light, and UV rays throughout the entire duration of treatment and for five days after treatment is stopped. Phototoxic reactions have occurred even with the use of sun screens and can occur following a single dose.[49]

A moderate prolongation of the QTc interval (approximate 2% incidence) occurs with sparfloxacin. The mean prolongation is about 10 msec. A small percent of patients (0.7%) had a clinically significant QTc interval prolongation of more than 500 msec. Torsades de pointes has been reported in patients receiving sparfloxacin with disopyramide and amiodarone. Consequently, the drug is contraindicated in patients who are taking agents (including terfenadine, disopyramide, amiodarone, and others) known to prolong the QTc interval, and in individuals with a known QTc prolongation.[49] Other side effects include diarrhea (4.6%), nausea (4.3%), and headache (4.2%).[49]

Sparfloxacin is supplied in 200 mg tablets. The initial dose is 400 mg on the first day as a loading dose, then 200 mg every 24 hours for a total of 10 days. In patients with renal impairment (creatinine clearance < 50 mL/min), the 400 mg loading dose is used, but the maintenance dose should be reduced to 200 mg every 48 hours for a total of 10 days.[49] Sparfloxacin can be taken with food but not with sulcrafate or antacids.

Both sparfloxacin and levofloxacin may be considered for the treatment of respiratory infections caused by penicillin-resistant *Streptococcus pneumoniae*.[53] Sparfloxacin has greater in vitro activity against this organism as well as more favorable pharma-

codynamics (i.e., plasma levels relative to minimum inhibitory concentrations) than levofloxacin,[54] but the potential for phototoxicity and prolongation of QTc must be weighed against the potential advantages in selected patient subgroups. Prudent use of these new agents are essential. With the emergence of drug-resistant *Streptococcus pneumoniae*, the rational use of antibiotics is paramount in limiting the spread of this organism. These new fluoroquinolones, if used appropriately, can provide a useful alternative to older agents against this organism. Sparfloxacin is priced in the same range as levofloxacin, clarithromycin, and cefuroxime axetil and somewhat more than azithromycin.

Non-Extended Spectrum Quinolones. The older quinolones still constitute the primary treatment modality for bacterial infections of the urinary tract. From an emergency medicine perspective, the non-extended spectrum quinolones such as ciprofloxacin still play a very important role in and can be considered reasonable first-line agents for the following conditions: prostatitis in older men, invasive bacterial diarrheas with prolonged duration of symptoms, complicated urinary tract infections, otitis external, diabetic vasculopathic ulcers, one-dose therapy for gonorrhea, and selected cases of osteomyelitis. Ciprofloxacin and ofloxacin have a wide variety of indications, while norfloxacin, lomefloxacin, and enoxacin are generally used only for infections of the urinary tract. More frequent use of quinolones has resulted in increasing resistance, which has been observed predominantly in methicillin-resistant staphylococci and *P. aeruginosa*.[55]

The quinolones are not presently recommended for use in patients younger than 18 years old or in pregnant or lactating women due to concerns over cartilage toxicity.[56] However, the quinolones may enjoy increased use in children if European safety data are further substantiated.[57] Because divalent and trivalent cations decrease quinolone absorption, concomitant antacids, calcium, sucralfate, iron, and zinc need to be avoided. The quinolones may decrease theophylline and caffeine metabolism by inhibiting the hepatic cytochrome P-4P-450 system, with enoxacin, ciprofloxacin, and norfloxacin being most often implicated.[55] Phototoxicity may occur most frequently with lomefloxacin and sparfloxacin.

Phosphonic Acids. Fosfomycin (Monurol®), a new single-dose antibiotic has been approved by the FDA for the treatment of uncomplicated urinary tract infections in women, but not in men. This new synthetic antibiotic inhibits cell synthesis by inactivating the enzyme enolpyruvyl transferase, which catalyzes one the early steps in cell wall synthesis. Extensively used in Europe since 1988, fosfomycin tromethamine represents the first in a new class of antibiotics that are derivatives of phosphonic acid. The drug is bactericidal against a wide range of common urinary tract pathogens and is well absorbed orally. A single dose results in high serum levels, which provides concentrations above the MIC for common urinary pathogens for up to 3.5 days. Supplied as a package of soluble granules that is mixed with water, fosfomycin is indicated for the treatment of uncomplicated UTIs (acute cystitis) in women, due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*, and there is generally little cross resistance between fosfomycin and other antibiotics.[59] It should be stressed, however, that in vitro data suggests that *Staphylococcus saprophyticus*, a common urinary pathogen, is resistant to fosfomycin.[60]

Fosfomycin received a Pregnancy Category B (i.e., no documented evidence of risk in humans), the same as amoxicillin and nitrofurantoin, while TMP/SMP and quinolones are in category C (i.e., risk cannot be ruled out and use in pregnancy not recommended). The most common side effect of fosfomycin is diarrhea (9%) which, on average, last for about two days.[61] Although the bacteriologic eradication rate with a single dose of fosfomycin (82%) is inferior to that of a seven-day course of ciprofloxacin (98%) or a 10-day course of TMP/SMX (98%), it is comparable to eradication rates seen with 3-day courses of commonly used antimicrobials.[59] Because metoclopramide lowers the serum concentration and urinary excretion of fosfomycin, coadministration of these drugs is not recommended.

From a practical standpoint, fosfomycin is supplied in orange flavored granules which are dissolved in 3-4 ounces of water taken as a single 3 gram dose. The medication should not be mixed with hot water and repeated daily doses do not appear to improve clinical success, but they do increase the incidence of adverse events. Fosfomycin may be taken without regard to food.[59]

The bacteriological cure rate for fosfomycin generally ranges between 69% to 96% as assessed 5-11 days post-treatment. In comparative clinical trials, fosfomycin was found to be less effective than seven days of ciprofloxacin (250 mg bid) and 10 days of TMP/SMX (960 mg daily) but was comparable to a seven-day course of nitrofurantoin (Macrodantin 100 mg bid).[59,60]

A small, nonblinded study (n = 36) suggests that fosfomycin may be more effective than low-dose TMP/SMX (960 mg) given for three days.[62] In a large, single-blind study (n =308), however, fosfomcyin was comparable to a single dose of TMP/SMX (1.92 g) and a single dose of ofloxacin (200 mg) in terms of bacteriologic rates.[63]

Although fosfomycin is the only FDA-approved, single-dose regimen, current clinical data indicates that it may be no more effective than a single dose of two double strength TMP/SMX. In current practice, most physicians opt for the improved cure rates associated with a three-day treatment of TMP/SMX (1 DS tablet bid × 3 days), which is often considered to be optimal treatment due to effectiveness and reduced relapse rates.[64,65] Unfortunately, comparative studies between this regimen and fosfomycin have not been reported. Fosfomycin costs about $21.04 per treatment) and, considering the other available, short-course alternatives, this drug should be reserved primarily for patients in whom TMP/SMX is not appropriate (e.g., sulfa allergy, bacterial resistance, and third trimester of pregnancy).

Clearly, fosfomycin offers an alternative to standard therapy for UTIs in women. But because its cure rates are no better than standard therapy, even standard single-dose therapy, it is best reserved for women with multiple drug allergies or patients who are compliance risks.

Macrolides. The newer macrolide antibiotics include the erythromycin analogs azithromycin and clarithromycin.[66,67] Compared to erythromycin, the major advantages of these antibiotics are significantly decreased gastrointestinal side effects, which

Table 3. Empiric Antibiotic Therapy for Bacterial Infections Commonly Encountered in the ED

Clinical Indication	Usual Pathogens	Primary Treatment	Alternative Treatment	Comments
ABDOMINAL				
Biliary tract	*Enterobacteriaceae,* Enterococci, anaerobes	Antipseudomonal penicillin + metronidazole ± aminoglycoside ***or*** Imipenem or beta-lactam/ beta-lactamase inhibitor	Third-generation cephalosporin + metronidazole ***or*** Aztreonam + clindamycin	Many acceptable regimens with requisite aerobic, anaerobic activity.
Peritonitis, appendicitis, diverticulitis, bowel perforation	Enterobacteriaceae, enterococci, anaerobes (occasionally *P. aeruginosa)*	Beta-lactam/ beta-lactamase inhibitor ***or*** Imipenem ***or*** many others	Third-generation cephalosporin + metronidazole ***or*** Aztreonam + clindamycin	Many acceptable regimens with requisite aerobic, anaerobic activity. Usually combination therapy with severe disease.
CENTRAL NERVOUS SYSTEM				
Meningitis	*S. pneumoniae,* meningococci, *L. monocytogenes*	Vancomycin + ceftriaxone ***or*** Cefotaxime + ampicillin	Penicillin allergy: vancomycin + chloramphenicol + TMP-SMX	Need for vancomycin dictated by incidence penicillin-resistant pneumococci.
COMMUNITY-ACQUIRED PNEUMONIA				
Outpatient, < 60, no co-morbid conditions	*S. pneumoniae, H. influenzae, M. pneumoniae*, *Legionella, Chlamydia*	A macrolide: azithromycin, clarithromycin, erythromycin (non-smokers and no COPD–see text)	Amoxicillin-clavulanate ***or*** doxycycline	
Outpatient, >60 and/or co-morbid conditions	*S. aureus,* gram-negative *Klebsiella, E. coli*	Amoxicillin/clavulanate ***or*** Extended-spectrum cephalosporin ***±*** *macrolide* ***or*** extend spectrum quinolone		
Hospitalized	As per both above	Azithromycin IV ***or*** Extended-spectrum cephalosporin IV + erythromycin IV ***or*** Levaquin IV	Substitute beta-lactam/ beta-lactamase inhibitor ***or*** imipenem ***or*** others for cephalosporin	
GASTROINTESTINAL				
Infectious diarrhea	*Shigella, Salmonella Campylobacter, E. coli*	Quinolone	TMP-SMX	
RESPIRATORY TRACT (UPPER)				
Acute otitis media	*Pneumococcus, Haemophilus, Moraxella,* occasionally group A strep,	Amoxicillin* ***or*** Azithromycin ***or*** Amoxicillin-clavulanate Extended-spectrum cephalosporin	TMP-SMX ***or*** Clarithromycin	*Amoxicillin failure = 10-15%

Table 3. Empiric Antibiotic Therapy for Bacterial Infections Commonly Encountered in the ED

Clinical Indication	Usual Pathogens	Primary Treatment	Alternative Treatment	Comments
Pharyngitis/tonsillitis	Beta-hemolytic strep (Group A, C, G) *A. haemolyticum,* nonbacterial	Benzathine penicillin G ***or*** Penicillin V ***or*** Erythromycin	Extended-spectrum cephalosporin ***or*** Clarithromycin, azithromycin	
Acute sinusitis	As per otitis media	TMP-SMX ***or*** Amoxicillin-clavulanate	Extended-spectrum cephalosporin ***or*** clarithromycin	
RESPIRATORY TRACT (LOWER)				
Acute bacterial exacerbation of chronic bronchitis (ABECB)	*Pneumococcus, Haemophilus, Moraxella*	TMP-SMX ***or*** Doxycycline ***or*** Azithromycin	Extended-spectrum cephalosporin ***or*** Clarithromycin, **or** Amoxicillin-clavulanate **or** Levofloxacin	
SEXUALLY TRANSMITTED DISEASES				
Uncomplicated gonorrhea	*N. gonorrhoeae*	Any single-dose regimen as per Table 7		
Uncomplicated nongonococcal urethritis, cervicitis	*C. trachomatis, Mycoplasma, Ureaplasma*	Azithromycin Doxycycline	Erythromycin Ofloxacin	
Pelvic inflammatory disease				
Outpatient	*Gonococcus, Chlamydia,* anaerobes, gram-negative streptococci	Ceftriaxone + doxycycline ***or*** azithromycin IV + oral therapy for total of 7 days ***or*** Ofloxacin + clindamycin ***or*** metronidazole may be added to any of the above regimens as required	Cefoxitin + probenecid + doxycycline	
Inpatient	As above	Cefoxitin/cefotetan + doxycycline **or** azithromycin IV ± metronidazole	Gentamicin + clindamycin	
SKIN AND SKIN STRUCTURE INFECTIONS				
Uncomplicated	*S. aureus,* Group A strep	Cephalexin Azithromycin	A macrolide Dicloxacillin	
Complicated	Polymicrobic	Amoxicillin-clavulanate	Quinolone + clindamycin TMP-SMX + clindamycin	
Diabetic foot	Polymicrobic: aerobic gram-positive, gram-negative, and anaerobes	Outpatient: ciprofloxacin + clindamycin	Hospitalized: beta-lactam/ beta-lactamase inhibitor, imipenem, other with equivalent activity	
URINARY TRACT INFECTIONS				
Uncomplicated	*E. coli*, *(S. saprophyticus:* cystitis), occasionally other *Enterobacteriaceae,* enterococcus	TMP-SMX Quinolone	Extended spectrum cephalosporin Amoxicillin-clavulanate Fosfomycin (cystitis)	
Chronic prostatitis	*Enterobacteriaceae*	Quinolone	TMP-SMX	

produce enhanced tolerance, improved bioavailability, higher tissue levels, pharmacokinetic features that permit less frequent dosing and better compliance, as well as enhanced activity against *H. influenzae*.[68,69] In particular, the long tissue half-life of azithromycin allows this antibiotic to be prescribed for a shorter duration (5 days) than comparable antibiotics given for the same indications. *(See Table 1.)*

Approved indications for the newer macrolides are listed in Table 2. A single 1 g dose of azithromycin has been shown to be as effective as seven days of doxycycline in the treatment of uncomplicated chlamydial cervicitis and urethritis.[70] The availability of one-dose, "cure here now" therapy offers substantial compliance advantages in the ED setting. With the recent introduction of a 1 g sachet pack of azithromycin, which is priced at about $10-15 at many institutions and clinics, the Centers for Disease Control and Prevention (CDC) has advocated azithromycin as a drug of choice for uncomplicated chlamydia cervicitis.[71] A one-time 2 g oral dose has also been approved for the treatment of urethritis and cervicitis caused by *Neisseria gonorrhea*.

In contrast to azithromycin, clarithromycin (and erythromycin) should not be given with terfenadine or astemizole because of the risk of ventricular tachycardia. Both erythromycin and clarithromycin may increase theophylline levels. Clarithromycin, which has a category C rating, is contraindicated in pregnancy because of fetal cardiovascular abnormalities discovered in animal toxicologic studies. Azithromycin, which has a category B rating, is appropriate for use in pregnant patients, but only when clinical findings indicate that antimicrobial treatment is warranted.

Because macrolides are the fastest-growing class of outpatient antimicrobials, comparing the advantages and disadvantages of these two antibiotics is an important issue for emergency practice. Given the cost differences between azithromycin and clarithromycin, as well as the improved compliance patterns associated with short-duration therapy, any rational approach to distinguishing between these agents must consider prescription, patient, and drug resistance barriers.

From the outset, it is fair to say that these newer macrolides, to a great degree, have supplanted the use of erythromycin in community-acquired infections of the lower respiratory tract. Although erythromycin, in particular, has been considered by some to be the antibiotic of choice for community-acquired pneumonia, its lack of efficacy against *H. influenzae*, as well as its adverse gastrointestinal side effects, potential for drug-drug interactions, and poor compliance profile are now recognized as clinically important liabilities in emergency practice. It is, however, effective against pneumococcal pneumonia, mycoplasma pneumonia, and many atypical infections, including Legionella. Food decreases the absorption of erythromycin, which interferes with drug metabolism, and the drug should be used with caution in patients on theophylline or warfarin. It should not be used concurrently with terfenadine.

From the perspective of emergency medicine practice—with its primary emphasis on providing definitive, cost-effective, compliance-promoting, and drug-drug-interaction-minimizing therapy—the newer macrolide antibiotics, which include both azithromycin and clarithromycin, have recently emerged as drugs of choice for outpatient management of community-acquired pneumonia, as well as otitis media.[72] When used as oral agents, they play a central role in ED-based management of pneumonia in otherwise healthy individuals who do not require hospitalization. Recently, however, the intravenous formulation of azithromycin has been approved for hospitalized patients (see below). Unlike penicillins, cephalosporins, and sulfa-based agents, these drugs have the advantage of showing in vitro activity against both atypical and bacterial offenders implicated in community-acquired pneumonia. The most common side effects include gastrointestinal upset and a metallic taste in the mouth which are more common in clarithromycin.

These agents also have the advantage of a simplified dosing schedule, especially azithromycin, which is given once daily for only five days (500 mg po on day 1 and 250 mg po qd on days 2-5). Clarithromycin requires a longer course of therapy and is more expensive. In general, the decision to use a macrolide such as azithromycin rather than erythromycin is based on weighing the increased cost of a course of therapy with azithromycin against its real-world advantages, which include a more convenient dosing schedule, its broader spectrum of coverage, its favorable drug interaction profile, and its decreased incidence of gastrointestinal side effects, which occur in 3-5% of patients taking a five-day, multiple-dose regimen.[73] The recent introduction of a new oral tablet formulation permits consumption of the antibiotic without regard to food ingestion.

Azithromycin. Since our last antibiotic update (*Emerg Med Reports* 1996;1:1-12), azithromycin has been approved in a palatable suspension formulation for the treatment of acute otitis media and pneumonia in children. The cost for a course of therapy is usually less than $30, and the once-daily, five-day course introduces compliance-enhancing features that, to a great degree, permit parental, day care, and grade school drug administration problems to be circumvented.[74] A well-accepted palatability profile, combined with an overall discontinuation rate of about 0.9%, are favorable as far as patient resistance is concerned.[75-77] When the five-day course of the suspension is used for treatment of otitis media, the reported incidences of side effects includes diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%).

From the perspective of drug resistance, the oral suspension of azithromycin is characterized by excellent in vitro coverage of beta-lactamase-producing *H. influenzae* and *M. catarrhalis*, as well as in vitro coverage of *S. pneumoniae*, for which the overall resistance rate is estimated to be about 5-7%.[75-77] Although this second-generation macrolide has been used widely in the adult population, azithromycin oral suspension for children only recently has become available for use by pediatric specialists in the United States.

In this regard, the clinical role of azithromycin in the ED, pediatric, and primary care setting is supported by rigorous clinical studies that have been published comparing the safety and efficacy of azithromycin to amoxicillin-clavulanate for the treatment of acute otitis media in children.[75,78,79] In these large trials, clinical cure rates of up to 87.5% are reported, and azithromycin was as effective as, but better tolerated than, amoxicillin-clavulanate for the treatment of acute otitis media in the pediatric age group.[74,78-80] Although azithromycin does not affect a single IV dose of theophylline, caution is advised if multiple doses of theophylline are used. Accordingly, pru-

Table 4. Empiric Antimicrobial Therapy of Choice for Outpatient Management of Community-Acquired Pneumonia*

PATIENT PROFILE/ETIOLOGIC AGENT	FIRST-LINE ANTIBIOTIC THERAPY	ALTERNATIVE TREATMENT REGIMEN
Otherwise healthy **< 60 years of age** [Empiric therapy]	Azithromycin 500 mg po day 1, 250 mg po daily days 2-5	Clarithromycin 500 mg po bid × 10 days **or** Erythromycin 500 mg po qid × 10 days **or** Levofloxacin‡ 500 mg po qd × 7-14 days
Otherwise healthy **> 60 years of age** [Empiric therapy]	Cefuroxime 250 mg po bid × 10 days **plus a** macrolide (i.e., azithromycin, clarithromycin, or erythromycin) **or** Levofloxacin‡ 500 mg po qd × 7-14 days **or** Sparfloxacin‡ mg po day 1, then 200 mg po qd days 2-10	Amoxicilin-clavulanate 875 mg po bid × 10 days **plus** a macrolide
Haemophilus influenzae [Targeted therapy, i.e., Dx confirmed]	Azithromycin 500 mg po day 1, then 250 mg po daily × 4 days	Clarithromycin 500 mg po bid ×10 days **or** TMP/SMX ds one tab po bid × 10 days
Mycoplasma pneumoniae [Targeted therapy, i.e., Dx confirmed]	Azithromycin 500 mg po day 1, 250 mg po daily days 2-5	Clarithromycin 250 mg bid × 14 days Erythromycin 500 mg po qid × 10-21 days
***Chlamydia pneumoniae* (TWAR)**	Azithromycin 500 mg po day 1, then 250 mg po qd × 4 days **or** Levofloxacin‡ 500 mg po × 7-14 days	Tetracycline 500 mg po qid × 14 days Erythromycin 500 mg po qid × 14 days
***Legionella* species**	Erythromycin 500 mg po qid × 14 days **or** Azithromycin IV **or** Levofloxacin 500 mg po qd × 14 days	Tetracycline 500 mg po qid × 14 days
	If lack of prompt clinical response, add: Rifampin 600 mg po bid × 14 days	

* These treatment recommendations are appropriate only for otherwise healthy patients with community-acquired pneumonia of mild enough severity that they are judged to be suitable candidates for outpatient therapy with oral antibiotics.

‡ These quinolones are restricted for use in patients ≥ 18 years of age.

dent clinical monitoring of theophylline levels is recommended in these patients. Monitoring of the prothrombin time is also urged in patients taking coumadin.

Like azithromycin, clarithromycin suspension also has been shown to produce comparable cure rates to amoxicillin-clavulanate.[7] Finally, the potential for drug-drug interactions between clarithromycin and theophylline, terfenadine, or astemizole requires caution. From a prescription resistance perspective, the cost for a course of therapy for clarithromycin is significantly more than it is for amoxicillin, trimethoprim-sulfamethoxazole, or azithromycin. Finally, with respect to medication compliance, BID dosing is less desirable than once-daily administration,[15] and unpleasant taste and palatability problems have been described for clarithromycin.[10,81,82]

From a practical clinical perspective, the newest and, perhaps most important, advance in the area of macrolide therapy is the availability of intravenous azithromycin for the management of hospitalized patients with community-acquired pneumonia (CAP) as well as pelvic inflammatory disease (PID).[83,84] Currently, azithromycin is the only advanced generation macrolide indicated for parenteral therapy in hospitalized patients with CAP due to *Chlamydia pneumoniae*, *H. influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Staphylococcus aureus*.

The comparative trials demonstrating clinical success (patients who were cured or improved at 10-14 days post-therapy) rates of about 77%—with concomitant bacteriologic response rates of about 96% for frequently isolated pathogens—with azithromycin in CAP were conducted in a wide variety of patients. These included a significant percentage who were 65 years of age or older, had an abnormal respiratory rate (> 30 breaths per minute), a PaO_2 less than 60 mm Hg and and/or BUN greater than 20 mg/dL. Many of these patients had concurrent diseases or syndromes, including emphysema, chronic obstructive airway obstruction, asthma, diabetes, and/or were cigarette smokers.[85]

As would be expected, the efficacy of this macrolide was compared to clinical outcomes with a cephalosporin used with or without erythromycin. In a randomized comparative investigation, therapy with intravenous azithromycin alone plus oral azithromycin was as effective as intravenous treatment with the designated "second-generation" cephalosporin, cefuroxime followed by oral cefuroxime axetil, with or without the addition of oral or intravenous erythromycin.[85]

Azithromycin dosing and administration schedules for hospi-

talized patients are different than for the five-day course used exclusively for outpatient management, and these differences should be noted by the ED physician. When this advanced generation macrolide is used for hospitalized patients with CAP, 2-5 days of therapy with azithromycin IV (500 mg once daily) followed by oral azithromycin (500 mg once daily to complete a total of 7-10 days of therapy) is clinically and bacteriologically effective. For patients requiring hospitalization, the initial 500mg intravenous dose of azithromycin may be given in the ED.

Interestingly, among all intent-to-treat patients with CAP receiving azithromycin evaluated in two studies, 24 were found to have *S. pneumoniae* bacteremia at baseline. Of these 24 patients, 19 (79%) achieved clinical cure, which was accompanied by eradication of the pathogen from the blood. Among the five patients considered to be clinical failures, three of the five had documented eradication of *S. pneumoniae* from the blood, and the remaining two did not have post-baseline cultures reported. All five patients had significant comorbid conditions that are predictive of poor outcomes, but none of the failures resulted in mortality.[85]

Like the oral formulation, IV azithromycin appears to be well-tolerated, with a low incidence of gastrointestinal adverse events (4.3% diarrhea, 3.9% nausea, 2.7% abdominal pain, 1.4% vomiting), minimal injection-site reactions (less than 12% combined injection-site pain and/or inflammation or infection), and a low incidence of discontinuation (1.2% discontinuation of IV therapy) due to drug-related adverse patient events or laboratory abnormalities.[85]

Matching Drugs with Bugs: Outcome-Effective Antibiotic Selection

Recommendations for the empiric antibiotic therapy of bacterial infections commonly encountered in the ED are listed in Table 3. In addition, selected comments on some of the common indications for antibiotic therapy follow.

Community-Acquired Pneumonia. A variety of antibiotics are available for outpatient management of pneumonia. Although the selection process can be daunting, as mentioned, a sensible approach to antibiotic selection in the ED for patients with pneumonia is provided by treatment categories for pneumonia generated by the Medical Section of the American Lung Association, and published under the auspices of the American Thoracic Society.[86] This classification scheme will not only help make clinical assessments useful for guiding therapy, but it is also predictive of ultimate prognosis and mortality outcome. *(See Table 4.)*

The most common pathogens responsible for causing community-acquired pneumonia include the typical bacteria: *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, as well as the atypical pathogens: *Mycoplasma, Legionella,* and *Chlamydia pneumoniae*.[87] *H. influenzae* and *M. catarrhalis* are both found more commonly in patients with COPD. Clinically and radiologically, it is difficult to differentiate between the typical and atypical pathogens; therefore, coverage against all these organisms may be necessary. In patients producing sputum-containing polymorphonuclear leukocytes, the sputum Gram's stain may contain a predominant organism to aid in the choice of empiric therapy. For most patients, therapy must be entirely empiric and is based on the expected pathogens.[88,89]

It must be understood that outpatient therapy for pneumonia in emergency practice is almost always empiric in nature. Hence, for the vast majority of otherwise healthy patients who have community-acquired pneumonia, but who do not have comorbid conditions and who are deemed well enough to be managed as outpatients, therapy directed at *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, and *M. catarrhalis* is appropriate. In these cases, one of the newer macrolides, such as azithromycin or clarithromycin, should be considered the initial agent of choice. The extended spectrum quinolones, levofloxacin and sparfloxacin, provide similar coverage and are also approved as initial therapy in this patient subgroup. Because of their excellent in vitro activity against *S. pneumoniae*, the use of levofloxacin and sparfloxacin should be strongly considered as initial therapy in urban areas where surveillance studies demonstrate a high incidence of macrolide-resistant *S. pneumoniae* species.

For the older patient with CAP who is considered stable enough to be managed as an outpatient, but in whom the bacterial pathogen list may also include gram-negative aerobic organisms, the combined use of a second-generation cephalosporin or amoxicillin-clavulanate plus a macrolide, or an advanced quinolone such as levofloxacin or sparfloxacin, is recommended. The advanced quinolones may be used as monotherapy, and, therefore, provide convenience and cost advantages in this high-risk subgroup. In those unusual cases in which a definitive, specific, etiologic diagnosis can be made (e.g., *Mycoplasma*, *C. pneumoniae*, *Legionella* species), agents with known activity against these organisms should be employed.

Some experts emphasize that in non-smoking adults without COPD (i.e., patients at a low risk for having *H. influenzae*), therapy with erythromycin should be strongly considered.[89] This is a matter of clinical judgment, but in any event, the newer macrolides, azithromycin and clarithromycin, are recommended in cases of erythromycin intolerance. In patients with COPD, TMP-SMX or doxycycline usually provides adequate coverage against *S. pneumoniae* and *H. influenzae*, but TMP-SMX will not cover atypical pathogens. Except for the newer quinolones such as levofloxacin and sparfloxacin, empiric use of the older quinolones is not recommended for treatment of community-acquired respiratory infections, primarily because of their variable activity against *S. pneumoniae* and overly broad gram-negative coverage. Although the older quinolones should generally not be used for the empiric treatment of community-acquired pneumonia, they may provide an alternative therapy for treatment of bronchiectasis, particularly when gram-negative organisms such as *Pseudomonas* are cultured from respiratory secretions.[90]

The use of levofloxacin as a first-line drug—in particular, as a substitute for the advanced generation macrolides—to treat uncomplicated community-acquired pneumonia or acute bacterial exacerbations of COPD in patients less than 60 years of age is more questionable and has become a matter of intense debate. Determining which of these antibiotics—macrolides vs. quinolones—should be considered "workhorse" drugs in the ED or primary care setting for treating bacterial "bugs and crud" above the belly button requires a thoughtful analysis that includes cost, convenience, spectrum, and potential for inducing resistance as part of the drug selection equation.

Table 5. Antibiotics for Acute Exacerbations of COPD

Antibiotic	Recommended Dose	Frequency	Duration
FIRST-LINE			
GENERICS			
Trimethoprim-sulfamethoxazole (Bactrim, Septra)	1 ds tab po	bid	7-14 d
Amoxicillin (Amoxil, Wymox)	500 mg	tid	7-14 d
Tetracycline	500 mg	qid	7-14 d
Doxycycline (Doryx, Vibramycin)	100 mg	bid	7-14 d
MACROLIDES/AZALIDES			
Azithromycin (Zithromax)	500 mg on 1st day, 250 mg qd × 4 days		5 d
Clarithromycin (Biaxin)	250 mg bid (for *S. pneumoniae/M. catarrhalis*)		
	500 mg bid (for *H. influenzae*)		7-14 d
QUINOLONES			
Levofloxacin (Levaquin)	500 mg qd		7-14 d
Sparfloxacin (Zagam)	400 mg qd day 1; 200 mg qd days 2-10		10d
SECOND-LINE			
QUINOLONES			
Ofloxacin (Floxin)	400 mg	bid	10 d
Ciprofloxacin (Cipro)	500 mg	bid	10 d
Lomefloxacin (Maxaquin)	400 mg	qd	10 d
CEPHALOSPORINS			
Cefixime (Suprax)	400 mg	qd	
	200 mg	bid	10 d
Cefprozil (Cefzil)	500 mg	bid	10 d
Cefaclor (Ceclor)	250 mg	tid	10 d
PENICILLINS			
Amoxicillin/clavulanate (Augmentin)	875 mg	bid	10 d

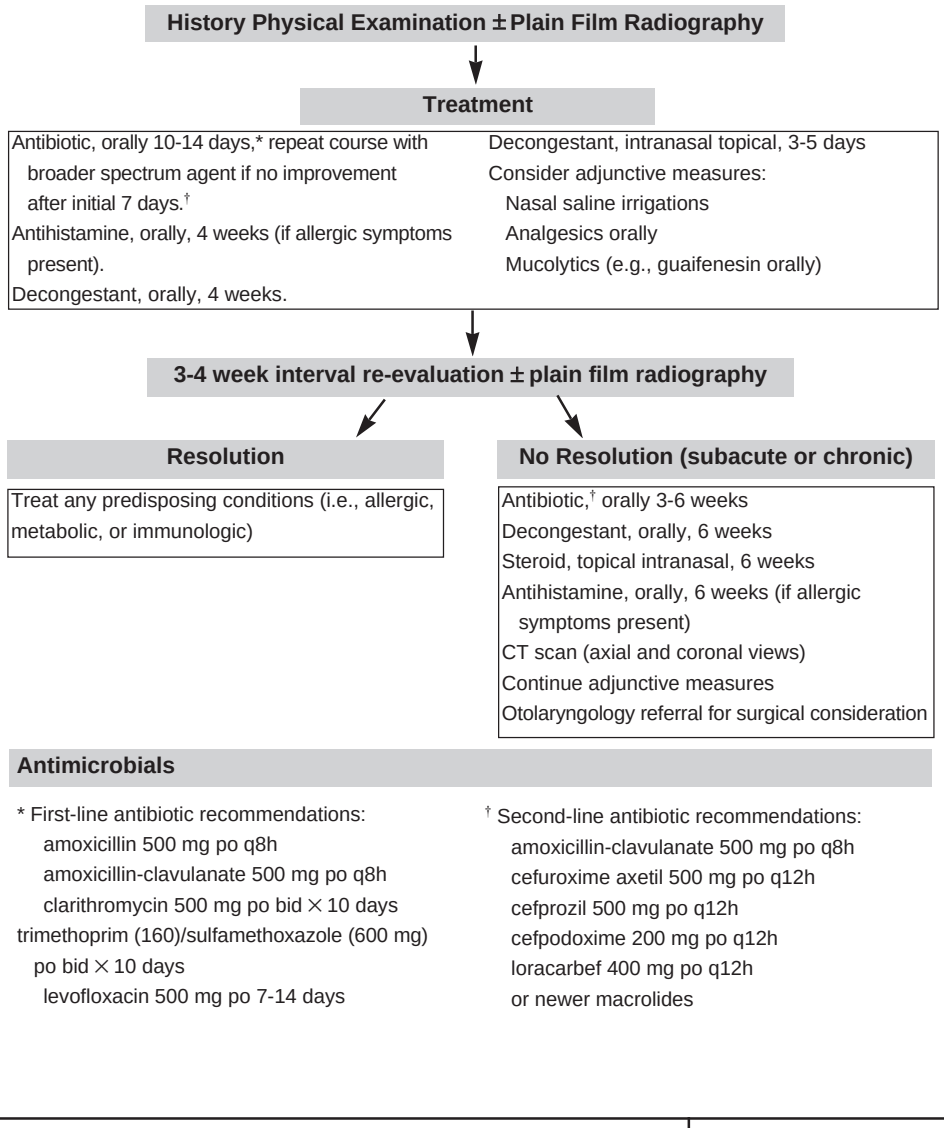
With its once-daily, minimum duration seven-day course, levofloxacin has dosing and duration advantages as compared to the macrolide clarithromycin, which requires 20 doses over 10 days. Moreover, the seven-day course of levofloxacin is comparatively priced with clarithromycin. Based on this analysis, but excluding the potential pitfalls associated with "broad" or, so-called, "over-extended" (i.e., not absolutely necessary gram-negative) spectrum of coverage, levofloxacin appears to provide a very reasonable alternative —and, perhaps, even a slight advantage—to clarithromycin in managing patients with CAP.

In the case of azithromycin, however, its five-day duration of therapy, $39-$42 cost per course of treatment, and targeted coverage of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *M. pneumoniae*, must be weighed against levofloxacin's 7-14 day duration of therapy, its $68-82 cost per treatment course, and the fact that its spectrum of coverage includes not only the appropriately targeted, aforementioned organisms commonly implicated in CAP, but extensive activity against gram-negative organisms, to which resistance may develop with indiscriminate use.

It appears, then, that when gram-negative coverage of *Klebsiella* and other species is not required, the advanced generation macrolide azithromycin may still represent a more prudent, less costly choice as initial therapy, especially in individuals less than 60 years of age. However, in the older patient, in whom gram-negative infection is more of a concern—as well, as in areas in which there is a high prevalence of *S. pneumoniae* resistance—the newer quinolones are an important alternative to two-drug combinations, especially in the elderly patient where spectrum of coverage may be especially important.

Finally, there is an increasing problem in the United States concerning the emergence of *S. pneumoniae* that is relatively resistance to penicillin and, less commonly, to extended-spectrum cephalosporins (see below). These isolates are often also resistant to macrolides, sulfonamides, and tetracyclines.[91-93] Except for vancomycin, the most favorable in vitro response rates to *S. pneumoniae* have been observed with the advanced macrolides and, more recently, with extended spectrum quinolones, especially sparfloxacin. Thus far, the majority of lower respiratory tract infections respond to standard therapy, though there have been profound implications for the empiric treatment of meningitis. Therapy for upper respiratory tract infections, such as sinusitis and otitis media, as well as for

Figure 1. Management of Uncomplicated Sinusitis



lower respiratory tract infections may be dramatically affected in the future if these mechanisms of resistance become more common.

Bacterial Exacerbations of Chronic Obstructive Pulmonary Disease (COPD). Chronic obstructive pulmonary disease (COPD) affects approximately 20% of all adults and is the fourth leading cause of death in the United States.[94] Exacerbations of COPD are usually manifested by an increase in cough, change in quantity or color of sputum, or worsening dyspnea and may lead to hospitalization. There are numerous possible causes of exacerbations of COPD but infection is one of the most common identifiable etiologies. As a result, antibiotics have become a mainstay in the of treatment of patients with this disorder. Despite the widespread use of antibiotics in this setting, their efficacy remains somewhat uncertain.

In a recent report, academic investigators performed a widespread literature search in order to conduct a meta-analysis to answer the question, "Are antibiotics beneficial in patients with COPD exacerbations?"[94] English language studies published in the last 40 years were included in the analysis if they were randomized trials comparing antibiotic to placebo in patients thought to be having an exacerbation of COPD and had follow-up for at least five days. Nine studies were included (230 studies were excluded for a variety of reasons) but there were no uniform outcome measures for all the trials.

These trials were conducted in both the outpatient and inpatient settings. The earliest trial included was from 1957 and the most recent was from 1992. Seven of the nine trials showed a benefit of antibiotics over placebo with the overall effect size indicating a small benefit in the antibiotic treated group. In six trials in which peak expiratory flow rates (PEFR) were one of the outcome measures, the summary effect size was also small, with a summary change in PEFR of 10.75 L/min in favor of the antibiotic treated group, which is small, but can be clinically significant, particularly in COPD patients with low baseline PEFR. Exacerbations of COPD are commonly encountered seen in the outpatient/ED setting and, not infrequently, lead to hospitalizations. Infection is believed to be a common cause of exacerbations, although they are often difficult to document definitively. Based on the evidence in this meta-analysis study, antibiotics should be used in this setting, although the benefit appears to be relatively small. Nevertheless, agents that cover common respiratory pathogens such as *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis,* and, perhaps, atypical organisms (chlamydiae, legionella) are reasonable for this problem. *(See Table 5.)*

The shortest and most convenient regimens include azithromycin or levofloxacin, whereas the least expensive regimens include TMP-SMX or doxycycline. In addition to antibiotics, avoidance of airway irritants (tobacco, allergens), use of bronchodilators and systemic or inhaled corticosteroids are mainstays in the treatment of patients with exacerbations of COPD.

Upper Respiratory Tract Infection. Although penicillin remains the drug of choice in the treatment of pharyngitis caused by *S. pyogenes*, it appears that the newer cephalosporins and macrolides may yield a superior bacteriologic eradication rate and, possibly, a decreased relapse rate.[95,96] Since the prevention of rheumatic fever requires eradication of the infecting Streptococcus, the newer cephalosporins and the macrolides are assumed to be at least as effective as penicillin in achieving this goal. The more convenient dosing schedule of these newer

Table 6. PPPD Approach to Selection of Oral Antibiotic Suspensions for Treatment of Acute Otitis Media in Children[3,25,26,54,66,67]

ORAL ANTIBIOTIC SUSPENSION (Generic name)	PRESCRIPTION RESISTANCE (Cost for course of therapy < $40)	PARENTAL RESISTANCE (Once-daily dosing)	PATIENT RESISTANCE (Palatability and GI effect profile considered extremely favorable)	DRUG RESISTANCE (Less than 20% of *S. pneumoniae* isolates from middle ear show in vitro resistance and drug shows adequate coverage of beta-lactamase-producing *H. influenzae* and *M. catarrhalis*)
Amoxicillin	++ ($6.02)	– (TID)	+	–
Amoxicillin-clavulanate	+ ($38.10)	± (BID)	– (diarrhea)	+
Azithromycin	+ ($28.40)	+	+	+
Cefaclor	+ ($38.20)	– (BID/TID)	+	±
Cefixime	– ($45.66)	+	+	±
Cefpodoxime	– ($54.00)	+	– (poor taste)	+
Cefprozil	– ($45.59)	± (BID)	– (poor taste)	+
Cefuroxime	– ($62.84)	± (BID)	+	+
Clarithromycin	– ($42.40)	± (BID)	– (poor taste)	+
Erythromycin-sulfisoxazole	+ ($22.77)	– (TID or QID)	– (poor taste, GI intolerance)	±
Loracarbef	– ($54.40)	± (BID)	+	+
Trimethoprim-sulfamethoxazole	++ ($4.36)	± (BID)	– (allergic reactions)	±

(+) Satisfies specific PPPD category criterion; (-) Does not usually satisfy specific PPPD category criterion; (±) Possibly satisfies PPPD category criterion

agents may enhance compliance.

The most common etiologies of acute sinusitis include: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and a variety of less common organisms. Many antibiotic regimens have been shown to yield the expected bacteriologic cure rate of greater than 90%.[97] Interestingly, a recent trial using TMP-SMX in the treatment of acute sinusitis indicates that a shorter treatment duration of three days may be as effective as a traditional 10-day course for selected patients with mild infections.[98] *(See Figure 1.)*

Otitis Media In Children. The most commonly isolated bacterial pathogens in both acute and recurrent otitis media are *S. pneumoniae*, *H. influenzae* (nontypable), and *M. catarrhalis*.[76,77] Although there are studies that show high spontaneous cure rates in mild to moderate cases of acute otitis media, treatment with antibiotics is still the standard of care in the United States. Unfortunately, drug resistance among bacteria involved in otitis media is rapidly emerging.[75,77] In this regard, beta-lactamase production is common among isolates of *H. influenzae* and *M. catarrhalis*, rendering about 30-50% of *H. influenzae* and up to 80% of *M. catarrhalis* isolates resistant to ampicillin.[99]

Although variable from patient to patient and region to region, these emerging resistance patterns may explain the failure rates associated with such traditional therapeutic measures as amoxicillin.[75,77] Accordingly, the evolution of antibiotic-resistant bacterial strains implicated in otitis media has fueled interest in alternatives to amoxicillin, which, primarily because of its cost, has been the traditional first-line agent for this infection, despite showing increasing resistance. This problem can be circumvented by adding a beta-lactamase inhibitor such as clavulanic acid to amoxicillin (i.e., amoxicillin/clavulanate) or by choosing alternative antibiotics, among them, azithromycin, loracarbef, and second-generation cephalosporins.

Without question, as previously emphasized in the case of CAP for adults, a most disturbing trend is the emergence of penicillin-resistant *S. pneumoniae*. Although the incidence of resistant strains demonstrates regional variations, the continued prevalence of *S. pneumoniae* as the principal etiologic agent in otitis media has important therapeutic implications, especially in light of the trend toward emergence of penicillin- and cephalosporin-resistant strains of this organism. From a clinical perspective, it should be emphasized that the development of penicillin-resistant strains has been associated with increased resistance to other beta-lactam antibiotics, including amoxicillin, cefaclor, cefuroxime, and cefixime, as well as the non-beta-lactam antibiotics TMP-SMX and erythromycin.[100,101]

Based on currently available studies, about 25% of *S. pneumoniae* isolates obtained by tympanocentesis from patients with otitis media in various regions of the United States demonstrated intermediate or complete resistance to penicillin. Currently, intermediate or complete resistance to the advanced macrolides, azithromycin and clarithromycin, has been identified in about 5-

Table 7. Single-Dose Therapy for Uncomplicated Gonorrhea

ANTIBIOTIC	DOSE*	COST†
Cefpodoxime proxetil	200 mg	$3.14
Cefixime	400 mg	$6.07
Ceftriaxone	250 mg IM	$10.71
Cefuroxime axetil	1000 mg	$12.22
Enoxacin	400 mg	$2.73
Ciprofloxacin‡	500 mg	$3.13
Ofloxacin	400 mg	$3.66
Norfloxacin	800 mg	$5.08
Azithromycin§	2 g	$17.21

* Oral unless otherwise stated
† Average wholesale price (AWP) (*1996 Red Book*. Montvale NJ: Medical Economics Data Production Co; 199)
‡ Not an approved indication, but widely used
§ Provides coverage of uncomplicated chlamydia cervicitis/ urethritis

8% of *S. pneumoniae* isolates, as compared to 10-25% of isolates shown to be resistant to such antibiotics as penicillin, amoxicillin, cefixime, TMP-SMX, and other cephalosporins.[75,76,77]

These findings suggest that in vitro resistance patterns to *S. pneumoniae* are one factor that should be considered in the selection process of an antibiotic for treatment of otitis media. *(See Table 6.)* The only antibiotic to which drug resistance has not been found is vancomycin.

Urinary Tract Infection. Cystitis, urethritis and pyelonephritis, and prostatitis are common infections managed in the primary care setting. An estimated 10-20% of women are afflicted at some point with a urinary tract infection (UTI) and the incidence in older men approaches that of women.[102] The development of new antibiotic agents, streamlining of the standard of care for young females with suspected UTI and the recognition that a wide array of clinical and microbiologic entities can present with dysuria, have led to a change in the approach to patients with UTI.

Acute cystitis and subclinical pyelonephritis are common in young females and are often impossible to distinguish clinically. Up to 25% of women presenting with the classic symptoms of lower UTIs actually suffer from "subclinical" pyelonephritis. *Enterobacteriaceae* (predominantly *E. coli*) account for 80% and *Staphylococcus saprophyticus* account for 10-15% of UTIs in young women when sexually transmitted pathogens are excluded. The precise etiology of UTIs in an individual patient may be difficult to determine. In one study, only 66% of young women presenting to a family practice setting with urinary tract symptoms could be assigned a specific microbiologic diagnosis despite an extensive work-up.[102]

In young women, acute cystitis and urethritis occur in the absence of classical criteria for bacteruria (10^5 bacteria per mL of urine) in as many as 50% of cases.[102-104] The constellation of dysuria, frequency and pyuria in the absence of "significant" bacteruria, has been termed the acute urethral syndrome. In many cases, this syndrome is caused by low level infections with *E. coli* (10^2-10^4 organisms per mL) or with a sexually transmitted pathogen such as *Chlamydia trachomatis*. The modern standard for a positive urine culture in a patient with dysuria is now widely accepted to be 10^2 rather than 10^5 organisms per mL.

Sexually transmitted pathogens can cause urethritis, vaginitis, and prostatitis, conditions that can clinically mimic the infections of classic uropathogens such as *E. coli*. Microorganisms including *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *C. trachomatis*, and *Ureaplasma urealyticum* are common offenders. Urethritis and epididymitis caused by sexually transmitted pathogens are increasingly common among promiscuous males, and UTI may be associated with HIV or herpes virus infection. With advancing age, the rate of UTI in males approaches that seen in females, and is often associated with prostate disease. Some unusual pathogens of iatrogenic origin are also found in the elderly. *Pseudomonas* and *Staphylococcus* species are associated with urinary tract manipulation, and enterococcus is found in patients who had previously received cephalosporin antibiotics.

Asymptomatic bacteruria is diagnosed when more than 10^5 colonies of a single bacterial species are recovered on two consecutive urine cultures in patients without symptoms. In most of these patients, antibiotic therapy does not yield any lasting benefit. During pregnancy however, asymptomatic bacteruria occurs in as many as 30% of women and commonly leads to full blown pyelonephritis if left untreated. Often, these infections are caused by *Streptococcus agalactiae*, a common flora of the female genitourinary tract that has been associated with premature delivery, neonatal sepsis, and postpartum endometritis. Asymptomatic bacteruria can also be found in as many as 33% of residents of skilled nursing facilities, and may be a nidus for sepsis in some. Antibiotic treatment in these patients is usually followed by relapse of bacteruria and it is therefore not routinely recommended.

The majority of uncomplicated urinary tract infections, the diagnosis of which will usually not require cultures, are caused by *E. coli*. However, insomuch as up to one-third of *E. coli* are resistant to amoxicillin, this antibiotic can no longer be recommended for treatment. In contrast, TMP-SMX is reliably active and is considered the treatment of choice. A recent trial concluded that a three-day regimen of TMP-SMX was more effective and less expensive than three days of nitrofurantoin, amoxicillin, or cefadroxil in the treatment of uncomplicated cystitis in women.[105] A new oral antibiotic, fosfomycin, is approved for single dose therapy, costs about $22, and has a success rate of about 70%.

In general, broader-spectrum agents offer no distinct advantage and are considerably more expensive than such agents as TMP-SMX. Nevertheless, it should be stressed that the quinolones play a major role in the treatment of urinary tract infection, especially when allergy or intolerance, bacterial resistance, or complicated infection is present. The optimum duration of therapy for uncomplicated cystitis appears to be three days; however, a seven-day course is indicated in patients with diabetes, in individuals with more than seven days of symptoms, a history of recent urinary tract infection, diaphragm use, age greater than 65 years, and in pregnant women.

As emphasized, for pyelonephritis, 14 days of therapy with TMP/SMZ, a fluoroquinolone, or a third-generation cephalosporin is indicated.[102,104] Treatment of asymptomatic bacteruria is unnecessary except during pregnancy. Pregnant women should have a urinalysis and culture at their first prenatal visit and urine dipsticks during the course of pregnancy. Asymptomatic bacteruria should be treated with 10 days of antibiotics and followed closely to assure that relapse does not occur. Antibiotics that are considered non-teratogenic include any of the beta-lactams, nitrofurantoin and sulfasoxazole. Trimethoprim and quinolone antibiotics should not be used in pregnant patients.

In sexually active patients, dysuria and pyuria may represent urethritis secondary to *N. gonorrhoeae* or chlamydia. A history of similar symptoms in a sexual partner or the presence of vaginal discharge may provide additional clues and prompt the appropriate genitourinary cultures. Some cases of acute urethral syndrome in females and most cases of epididymitis in young males are caused by chlamydia, which can be effectively treated with a seven-day course of doxycycline (100 mg bid). Trimethoprim and the fluoroquinolones have excellent penetration into inflamed prostatic tissue, making them excellent choices in elderly males where recurrent UTI is often associated with prostatitis. Nevertheless, relapses are common even after a month of antibiotic therapy.

Recurrent episodes of UTI may require a urologic evaluation for underlying problems such as urinary tract obstruction or stone disease. If no precipitating factors are discovered, prophylactic therapy should be considered. A nightly dose of 50 mg nitrofurantoin or 1 DS TMP/SMZ every other night will prevent recurrence in 90% of such patients. In a randomized, double-blind, placebo-controlled trial over eight months involving 93 postmenopausal women, investigators demonstrated that topical, intravaginal estrogen cream (0.5 mg estriol cream once each night for 2 weeks followed by 2 times per week for 8 months) led to a profound reduction in the rate of recurrent UTI and overall antibiotic use.[102,104,106] The mechanism appeared to be related to favorable alterations in vaginal pH and vaginal bacterial flora with increased presence of lactobacilli and reduced presence of *Enterobacteriaceae*.

Sexually Transmitted Diseases. Uncomplicated gonorrhea is treated with single-dose therapy. There are a variety of effective regimens based on quinolones, cephalosporins, and the macrolide azithromycin that vary considerably in cost. *(See Table 7.)* Chlamydia must always be empirically treated along with gonorrhea. The importance of effective communication in enhancing compliance with medication regimens cannot be overemphasized.[103] Current standards of care for the sexually transmitted diseases have been recommended by the CDC.[71] Because significant noncompliance has been reported with doxycycline, one-dose therapeutic modalities—azithromycin 1 gm po once for uncomplicated chlamydial infection and a choice of several agents for uncomplicated GC—are preferred. *(See Table 7.)*

The chlamydia problem deserves special attention. From an emergency therapeutics perspective, what is instructive about the chlamydial epidemic is the fact that, to a significant extent, it has grown significantly, in large part because of poor compliance with the traditional, seven-day bid doxcycline regimen, which has been the weak link between the prescription pad and optimal clinical outcome.[108] In one "real world" study, only 65% of all patients prescribed a seven-day course of doxycycline therapy reported sufficient intake of the antimicrobial to achieve clinical cure of their chlamydial infection.[108-110] When this occurs, a significant percentage of patients will return for retreatment because of noncompliance-mediated therapeutic failures. In addition, these patients are at risk for infecting other partners who must also access the healthcare system for treatment. The end result is "turnstyle STDs," a phenomenon in which pharmacologic reservicing for STDs and PID is required because of therapeutic failures associated with inadequate adherence to medication regimens. These observations strongly support the use of single dose therapy given under supervision, on site, in the ED or clinic, for treatment of uncomplicated chlamydial infections.

Pelvic Inflammatory Disease. Frequently managed in the ED setting, pelvic inflammatory disease (PID) is a term that is most commonly used to describe infection of the uterus, fallopian tubes, and adjacent pelvic structures that is not associated with surgery or pregnancy. An estimated 1 million women per year are diagnosed with PID, a condition that is particularly

Table 8. Treatment of Uncomplicated Chlamydia*

FIRST-LINE THERAPY	ALTERNATIVE THERAPY
Azithromycin 1 g po once (This is the only single-dose therapy for chlamydia approved by the CDC.)	Erythromycin base 500 mg po qid × 7 days
or Doxycycline 100 mg po bid × 7-10 days (contraindicated in pregnancy)	**or** Erythromycin ethylsuccinate 800 mg po qid × 7 days
	or Tetracycline 500 mg po qid × 10-14 days (Although effective, compliance is less than adequate, and the drug is contraindicated in pregnancy.)
	or Ofloxacin 300 mg po bid × 7-10 days (contraindicated in pregnancy and in patients < 18 years)

Adapted from: McCormack WM. Pelvic inflammatory disease. *N Engl J Med* 1994;330:115-119; Therapy for sexually transmitted diseases. *Med Lett* 1994;36:1-4; Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines. *MMWR Morb Mortal Wkly Rep* 1993;42(number RR-14):i-102; Sweet RL, et al. Evaluation of new anti-infective agents for the treatment of acute pelvic inflammatory disease. *Clin Infect Dis* 1992;15(suppl):S33-42.

*A thorough discussion of the diagnosis and management of gonorrhea, chlamydia, and pelvic inflammatory disease appears in a previous issue of *Emergency Medicine Reports* (*Emerg Med Rep* 1994;15:251-260).

common and problematic among lower socioeconomic groups in urban areas.[110-113]

In addition to the acute manifestations of the infection, long-term sequelae such as ectopic pregnancy and infertility occur in 25% of cases.[109-111] In 1994, the direct and indirect costs of the disease and its complications were estimated to be greater than $4 billion. In view of the impact of this infection, a systematic approach to diagnosis and therapy is mandatory for all emergency and primary care practitioners who encounter patients with this condition and its related complications.

In virtually all cases, PID results from from ascending spread of organisms from the cervix and vagina to the upper genital tract. Sexual transmission of *Neisseria gonorrhea* and/or *Chlamydia trachomatis* account for more than half of all cases of PID, but *H. hominis* and other organisms have also been implicated.[110-112] *N. gonorrhea* is the major cause of PID in urban areas, where gonococcal infection is prevalent, whereas *C. trachomatis* is responsible for a greater proportion of cases among college students, in whom gonococcal infection is less common. Organisms such as *E. coli* and other enteric pathogens, as well as pathogens from the vaginal flora, also may cause PID, particularly when the normal vaginal flora (lactobacilli) are supplanted with other organisms. However, infection in the upper genital tract does not always result in clinically recognizable disease; indeed, many women with adverse sequelae associated with PID, such as infertility, have no known history of the disease.[110-112]

In one prospective study, infertility due to tubal occlusion occurred in 8% of women after one episode of PID, in 19.5% after two episodes, and in 40% after three or more episodes.[106] Furthermore, as previously mentioned, many cases of PID are clinically silent, but as many as 70% of women who are infertile due to tubal obstruction have serum antibodies against chlamydia vs. only about 25% of women who are infertile for other reasons.[109,111,113]

A high index of suspicion and a low threshold for initiating treatment are important for facilitating detection and appropriate management. This approach should be applied to all women of child-bearing age with pelvic pain. Although laparoscopic visualization of inflamed fallopian tubes and pelvic structures is possible and, according to some experts, serves as a "gold standard" for the diagnosis, it is seldom practical. As a rule, the emergency physician must initiate antibiotic therapy on clinical grounds, despite its limitations. In addition to the clinical symptoms, lower abdominal tenderness, adnexal tenderness, and pain on manipulation of the cervix are present in physical examination in up to 90% of women.[110,112,113] Other manifestations, such as elevated erythrocyte sedimentation rate or C-reactive protein and abnormal vaginal discharge vary widely in frequency. At present, there are no effective ways to detect clinically silent disease.

Because new and highly effective treatment regimens have been introduced for PID, emergency physicians now have a number of therapeutic options available for managing these problematic—and, frequently, poorly compliant— patients with STDs and PID.[114-116] In this regard, the CDC recommend a number of possible regimens, most of which mandate the use of a broad-spectrum cephalosporin administered parenterally (initially) along with an oral agent effective against chlamydia such as doxycycline. Commonly used regimens for inpatient treatment of PID include the combination of cefoxitin, ceftriaxone, or cefotetan plus doxycycline; plus intravenous metronidazole followed by oral therapy with metronidazole plus doxycycline; gentamicin plus clindamycin; and intravenous ampicillin-sulbactam plus doxycycline.

As previously described, the oral formulation of azithromycin has been indicated for uncomplicated urethral and endocervical chlamydial infections and offers the unique advantage of efficacy with a single dose of 1 g po. Recently, however, efficacy and safety—as well as FDA approval—have been established for intravenous azithromycin therapy followed by oral azithromycin for the treatment of PID.

One study evaluated results in a total of 221 women with PID treated with the following regimens: 1) azithromycin monotherapy (administered as 500 mg IV as the initial dose on day 1, followed by 250 mg daily for 6 additional days); 2) azithromycin in combination with metronidazole; and 3) metronidazole (either intravenous metronidazole 500 mg bid on day 1 followed by oral administration of 500 mg bid for 11 days or oral administration of 500 mg bid for 12 days), plus doxycycline (100 mg po bid × 14 days), *plus* cefoxitin (2 gm IV or IM) with probenecid 1 g on the first day of treatment.[83,85]

In an intent-to-treat analysis conducted 15 days after therapy with these regimens, 93% of the patients receiving azithromycin alone, 94% of patients receiving azithromycin plus metronidazole, and 93% of those receiving the triad of cefoxitin, doxycycline, and metronidazole were either cured or improved.[85] The bacteriologic eradication rates for all all three regimens were in the 93-95% range. Azithromycin was well-tolerated in patients with PID. The most common side effects were diarrhea (8.5%) and nausea (6.6%). The addition of metronidazole to azithromycin increased slightly the incidence of gastrointestinal side effects, with 10.3% reporting nausea, 3.7% abdominal pain, and 2.8% vomiting.[85]

Based on this data, azithromycin IV (500 mg qd for 1 or 2 days) followed by oral azithromycin 250 mg po qd to complete a total of seven days of therapy should be considered a primary treatment modality for managing patients who require initial intravenous therapy for PID caused by *C. trachomatis*, *N. gonorrhoeae*, or *M. hominis*. The timing of the switch from intravenous to oral therapy should be made by the physician, who should make this decision based on clinical parameters. Moreover, it should be stressed that when anaerobic infection is strongly suspected to play an etiologic role in any individual patient with PID, the ED physician should combine an antimicrobial agent such as metronidazole that provides anaerobic coverage along with azithromycin.

Although many patients with PID—especially those who appear to be systemically toxic, have abdominal rebound tenderness, have WBC counts greater than 15,000, have a unilateral mass suggestive of tubo-ovarian abscess, have a history or profile indicating risk for poor medication compliance, are in the adolescent age group, and those in whom preservation of fertility is a high priority—will require hospitalization, a significant percentage can be treated with initial IV or IM therapy in the ED, followed by oral therapy out of the hospital to complete the antimicrobial course.

Current options for out-of-hospital management of mild

PID include the well-established regimen of ceftriaxone 500 mg IM, followed by doxycycline 100 mg po bid × 14 days with or without metronidazole 500 mg po tid for 10-14 days. With approval of the azithromycin IV/oral sequenced combination regimen outlined above, it is now possible to streamline therapy for PID into a seven day course, and substantially reduce the number of oral doses required to complete the treatment course. The practical implications are as follows: If, on the basis of the clinical findings, the ED physician deems that a patient with mild PID can be managed out of the hospital, and that a single intravenous dose of azithromycin in the ED is sufficient prior to oral therapy, then azithromycin should be administered as an infusion at a rate of 2 mg/mL over 1 hour, or 1 mg/mL over three hours. Azithromycin IV should always be infused over a period of not less than one hour, and should never be administered by bolus or intramuscular injection. If patients with PID have signs and symptoms that suggest the need for more than one intravenous dose, hospitalization will usually be necessary.

The one-hour minimum infusion time required for this antibiotic is not as convenient as the IM route of administration required for the ceftriaxone (plus oral doxycycline) regimen. However, the post-parenteral therapy phase of the azithromycin treatment regimen (which requires only an additional 6 days of oral therapy following the IV dose) is considerably more convenient and compliance-enhancing—both with respect to daily dose frequency and duration of therapy—than the ceftriaxone regimen, which requires consolidation with 28 oral doses of doxycycline over a 14-day period. In a patient population at high risk for noncompliance, the azithromycin regimen offers a potential window of opportunity that should be considered in this difficult patient population.

All women seen in the ED with suspected or confirmed PID require a pregnancy test to determine appropriate management. If present, intrauterine devices should be removed once antibiotic therapy is initiated. Close follow-up of outpatients within 24-48 hours after treatment is started is important. Failure to improve indicates the need for reassessment of the diagnosis (using laparoscopy, ultrasonography, or hospitalization) rather than a change in antibiotic therapy.

Male sexual partners of patients with PID need to be evaluated; this should include examination for sexually transmitted infections other than chlamydial and gonococcal disease, although, as a minimum, they must be treated for these two infections. Women who have had PID should be advised against the use of intrauterine devices and to protect themselves as much as possible against subsequent sexually transmitted infection to reduce their likelihood of infertility and other long-term sequelae. In women with concomitant HIV infection, hospitalization and intravenous therapy are indicated.

Skin and Skin Structure Infections. The majority of uncomplicated skin and skin structure infections are caused by staphylococci and streptococci. Conventional treatment with cephalexin or dicloxacillin is highly effective; the newer agents should be reserved for resistant organisms.[117] Diabetic foot infections are more frequently polymicrobial, and common offending agents include anaerobes, gram-positive organisms, and gram-negative bacteria. Consequently, treatment is often empiric. In the outpatient setting, an oral quinolone (plus clindamycin when anaerobic and enhanced gram-positive activity is required) is an appropriate first-line agent.[118]

Summary

The newer oral cephalosporins, quinolones, and macrolides often have an extended in vitro spectrum of activity, more desirable side-effect profiles, and improved pharmacokinetic patterns compared to older, conventional antibiotics. Frequently, there is a price to pay for such advances and advantages, including higher acquisition cost and increasing selective pressure for the emergence of resistant organisms. Although many common bacterial infections can usually be treated successfully with standard agents at a reduced cost, there are many circumstances when total outcome costs will be reduced by employing antibiotics with a shorter duration of therapy, less frequent daily dosing, and a more targeted spectrum of coverage that encompasses the most likely etiologic agents in specific patient subgroups. In particular, patient compliance with medications must always be considered when prescribing antibiotics, especially in the ED setting.

References

1. Temafloxacin withdrawn. *FDA Med Bull* 1992;22:4.
2. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: Review of 95 cases. *Clin Infect Dis* 1994;18:946-950.
3. Cockburn J, Gibberd RW, Reid AL, et al. Determinants of non-compliance with short term antibiotic regimens. *BMJ* 1987;295:814-818.
4. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990;150:1881-1884.
5. Sanson-Fisher R, Bowman J, Armstrong, S. Factors affecting non-adherence with antibiotics. *Diagn Microbiol Infect Dis* 1992;15:103S-109S.
6. Neu HC. The crisis in antibiotic resistance. *Science* 1992;257: 1064-1073.
7. Murray BE. New aspects of antimicrobial resistance and the resulting therapeutic dilemmas. *J Infect Dis* 1991;163:1185-1194.
8. Chater RW. Dosing tips for tots. *Am Pharm* 1993;NS33:55-56.
9. Finney JW, Friman PC, Rapoff MA, et al. Improving compliance with antibiotic regimens for otitis media: Randomized clinical trial in a pediatric clinic. *Am J Dis Child* 1985;139:89-95.
10. Demers DM, Scotik Chan D, Bass JW. Antimicrobial drug suspensions: a blinded comparison of taste of twelve pediatric drugs including cefixime, cefpodoxime, cefprozil, and loracarbef. *Pediatr Infect Dis J* 1994:13:87-89.
11. Chinburapa V, Larson LN. The importance of side effects and outcomes in differentiating between prescription drug products. *J Clin Pharm Ther* 1992;17:333-342.
12. Anonymous. Writing prescription instructions. *Can Med Assoc J* 1991;44:647-648.
13. Coleman TJ. Non-redemption of prescriptions. *BMJ* 1994;308:135.
14. Roth HP, Caron HS. Accuracy of doctor's estimates and patients' statements on adherence to a drug regimen. *Clin Pharm Ther* 1978;23:361-370.
15. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990;150:1881-1884.

16. Greenbery RN. Overview of patient compliance with medication dosing: A literature review. *Clin Ther* 1984;6:592-599.
17. Bluestone CD, Klein JO. Management. In: *Otitis Media in Infants and Children.* Philadelphia: WB Saunders; 1988:121-201.
18. Jacoby GA, Archer GL. New mechanisms of bacterial resistance to antimicrobial agents. *N Engl J Med* 1991;324:601-612.
19. PÈchËre JC. Antibiotic resistance is selected primarily in our patients. *Infect Control Hosp Epidemiol* 1994;15:472-477.
20. McCaig LF, Hughes JM. Trends in antimicrobial prescribing among office-based physicians in the United States. *JAMA* 1995;272:214-219.
21. Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis? *Lancet* 1995;345:665-666.
22. Saint S, Bent S, Vittinghoff E, et al. Antibiotics in chronic obstructive pulmonary disease exacerbations. *JAMA* 1995;273:957-960.
23. Saxon A. Antibiotic choices for the penicillin-allergic patient. *Postgrad Med* 1987;37:1175-1180.
24. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995;74:167-170.
25. Cefuroxime-axetil. *Med Lett Drugs Ther* 1988;30:57-60.
26. Cefprozil. *Med Lett Drugs Ther* 1992;34:63-64.
27. Loracarbef. *Med Lett Drugs Ther* 1992;34:87-88.
28. Nadelman RB, Luger SW, Frank E. et al. A comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. *Ann Intern Med* 1992;117:273-280.
29. Cefixime. *Med Lett Drugs Ther* 1989;31:73-75.
30. Cefpodoxime proxetil. *Med Lett Drugs Ther* 1992;34:107-108.
31. Vantin (Cefpodoxime proxetil) Prescribing Information. Kalamazoo, MI: Upjohn Co; 1992.
32. Handsfield HH, McCormack WM, Hook EW, et al. A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. *N Engl J Med* 1991;325:1337-1341.
33. Novak E, Paxton LM, Tubbs HJ, et al. Orally administered cefpodoxime proxetil for treatment of uncomplicated gonococcal urethritis in males: A dose-response study. *Antimicrob Agents Chemother* 1992;36:1764-1765.
34. Ciprofloxacin. *Med Lett Drugs Ther* 1988;30:11-13.
35. Ofloxacin. *Med Lett Drugs Ther* 1991;33:71-73.
36. Mayer KH, Ellal JA. Lomefloxacin: Microbiologic assessment and unique properties. *Am J Med* 1992;92:58S-62S.
37. Enoxacin. *Med Lett Drugs Ther* 1992;34:103-105.
38. Cooper B, Lawer M. Pneumococcal bacteremia during ciprofloxacin therapy for pneumococcal pneumonia. *Am J Med* 1989;87:475.
39. Gordon JJ, Kaufman CA. Superinfections with Streptococcus pneumoniae during therapy with ciprofloxacin. *Am J Med* 1990;89:383-384.
40. Levaquin Product Information. Ortho-McNeil Pharmaceuticals. January 1997.
41. Flynn CM, et al. *J Chemother* 1996;8:411-415.
42. Dholakia N, et al. *Antimicrob Agents Chemother* 1994;38:848-852.
43. *Med Lett* 1996;38:25-34.(d) references
44. DeAbate LA, et al. *Respir Care* 1997;42:206-213.
45. Adelglass J, et al. Abstr Infect Dis Soc Am 1996;34. 34th Annual Meeting Infectious Disease Society of America, New Orleans, Louisiana. September 18-20, 1996.
46. Habib MP, et al. Abstr Intersci Conf Antimicrob Agents Chemother 1996;36. Abstract L002. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. New Orleans, Louisiana. September 15-18, 1996.
47. File TM, et al. Abstr Intersci Conf Antimicrob Agents Chemother 1996;36. Abstract L001 (LM1). 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. New Orleans, Louisiana. September 15-18, 1996.
48. Goa KL, et al. *Drugs* 1997;53:700-725.
49. Zagam Product Information. Rhone-Poulenc Rorer. January 1997.
50. Portier H, et al. *J Antimicrob Chemother* 1996;37 (Suppl. A):83-91.
51. Lode H, et al. *Eur Respir J* 1995;8:1999-2007.
52. Allegra L, et al. *J Antimicrob Chemother* 1996;37 (Suppl. A):93-104.
53. *Med Lett* 1997;39:41-43.
54. Stein GE. *CID* 1996;23 (Suppl. 1):19-24.
55. Jones R. Fluoroquinolone resistance: An evolving national problem or just a problem for some physicians? *Diagn Microbiol Infect Dis* 1992;15:177-179.
56. Gough AW, Kasali OB, Sigler RE, et al. Quinolone arthropathyóacute toxicity to immature articular cartilage. *Toxicol Pathol* 1992;20:436-450.
57. Schaad UB, Wedgewood J. Lack of quinolone-induced arthropathy in children. *J Antimicrob Chemother* 1992;30:414-416.
58. Rodvold KA, Piscitelli SC. New oral macrolide and fluoroquinolone antibiotics: An overview of pharmacokinetics, interactions, and safety. *Clin Infect Dis* 1993;17:S192-S199.
59. Monurol Product Information. Forest Pharmaceuticals, Inc. January 1997.
60. Patel SS, et al. *Drugs* 1997;53(4):637-656.
61. FDC Reports. The Pink Sheet. December 23, 1996.
62. Crocchiolo P, et al. *Chemotherapy* 1990;36 Suppl 1:37-40.
63. Naber KG, et al. *Infection* 1990;18 Suppl 2:S70-76.
64. Stamm WE, et al. *N Engl J Med* 1993;329:1328-1334.
65. *Med Lett.* 1996;38:25-34.
66. Clarithromycin and azithromycin. *Med Lett Drugs Ther* 1992;34:45-47.
67. Whitman MS, Tunkel AR. Azithromycin and clarithromycin: Overview and comparison with erythromycin. *Infect Control Hosp Epidemiol* 1992;12:357-368.
68. Periti P, Mazzei T, Mini E, et al. Adverse effects of macrolide antibiotics. *Drug Safety* 1993;9:346-364.
69. Piscitelli SC, Danziger LH, Rodwold KA. Clarithromycin and azithromycin: New macrolide antibiotics. *Clin Pharm* 1992;11:137-152.
70. Martin DH, Mroczkowski TF, Dalu ZA. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. *N Engl J Med* 1992;327:921-925.
71. Centers for Disease Control and Prevention: 1993 Sexually Transmitted Diseases Treatment Guidelines. *MMWR Morb Mortal Wkly Rep* 1993;42(RR-14):1-102.
72. Watt B, Collee JG. Bacterial challenges and evolving antibacterial drug strategy. *Postgrad Med J* 1992;68:6-21.
73. Pfizer, Inc. Azithromycin package insert.
74. Khurana CM. Issues concerning antibiotic use in child care settings. *Pediatr Infect Dis J* 1995;14:S34-38.
75. Neu HC. Otitis media: Antibiotic resistance of causative pathogens and treatment alternatives. *Pediatr Infect Dis J*

1995;14:S51-56.
76. Data on file. New York. Pfizer, Inc.
77. Barry AL, et al. In vitro activity of 12 orally administered antibiotics against four species of respiratory pathogens from US medical centers in 1992 and 1993. *Antimicrob Agents Chemother* 1994;38:2419-2425.
78. Hopkins SJ, Williams D. Clinical tolerability and safety of azithromycin in children. *Pediatr Infect Dis J* 1995;14:S87-91.
79. Khurana C, McLinn S, Block S, et al. Trial of Azithromycin (AZ) vs Augmentin (AUG) for treatment of acute otitis media (AOM) [Abstract M61-64 Presented at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, FL, October 4-7, 1994.
80. Mclinn S. Double blind and open label studies of azithromycin in the management of acute otitis media in children: A clinical review. *Pediatr Infect Dis J* 1995;14:S62-66.
81. Nelson, JD. Clinical importance of compliance and patient intolerance. *Infect Dis Clin Pract* 1994;3:158-160.
82. Schentag JJ. Antibiotic treatment of acute otitis media in children: Dosing consideration. *Pediatr Infect Dis J* 1995;14:S30-33.
83. Pfizer product mongraph. Azithromycin for IV injection
84. Zimmerman T, Reidel K-D, Laufen H, et al. Intravenous toleration of azithromycin in comparison to clarithromycin and erythromycin. In Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society Microbiology; 1996:16 Abstract A82.
85. Data on file, Pfizer, Inc. New York, NY
86. American Thoracic Society, Medical Section of the American Lung Association. *Am Rev Respir Dis* 1993;148:1418-1426.
87. Fang G-D, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. *Medicine* 1990;69:307-316.
88. LaForce FM. Antibacterial therapy for lower respiratory tract infections in adults: A review. *Clin Infect Dis* 1992;14:S233-S237.
89. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis* 1993;148:1418-1426.
90. Thys JP, Jacobs F, Byl B. Role of quinolones in the treatment of bronchopulmonary infections, particularly pneumococcal and community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 1991; 10:304-315.
91. Jacoby GA. Prevalence and resistance mechanisms of common bacterial respiratory pathogens. *Clin Infect Dis* 1994;951-957.
92. Friedland IR. Therapy of penicillin and cephalosporin-resistant pneumococcal infections. *Ann Intern Med* 1993;25:451-455.
93. Steele RW. Drug-resistant pneumococci: What to expect, what to do. *J Resp Dis* 1995;16:624-633.
94. Saint S, et al. Antibiotics in chronic obstructive pulmonary disease exacerbations. *JAMA* 1995;273:957-960.
95. Pichichero ME. Group A streptococcal tonsillopharyngitis: Cost-effective diagnosis and treatment. *Ann Emerg Med* 1995;25:390-403.
96. Vukmir RB. Adult and pediatric pharyngitis: A review. *J Emerg Med* 1992;10:607-616.
97. Gwaltney JM Jr, Scheld WM, Sande MA et al. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a 15-year experience at the University of Virginia and review of other selected studies. *J Allergy Clin Immunol* 1992;90:457-462.
98. Williams JW, Holleman DR, Samsa GP, et al. Randomized controlled trial of 3 vs. 10 days of trimethoprim/sulfamethoxazole for acute maxillary sinusitis. *JAMA* 1995;273:1015-1021.
99. Jacoby GA. Prevalence and resistance mechanisms of common bacterial respiratory pathogens. *Clin Infect Dis* 1994;18:951-957.
100. Caputo GM, Singer M, White S, et al. Infections due to antibiotic-resistant gram-positive cocci. *J Gen Intern Med* 1993;8:626-634s.
101. Friedland IR, McCracken GH. Management of infections caused by antibiotic-resistant Streptococcus pneumoniae. *N Engl J Med*
102. Faro S. New considerations in treatment of urinary tract infections in adults. *Urology* 1992;39:1-11.
103. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993; 329:753-756
104. Arav–Boger R, et al. Urinary tract infections with low and high colony counts in young women. Spontaneous remission and single–dose vs multiple–day treatment. *Arch Int Med* 1994; 154:300–304.
105. Hooton TM, Winter C, Tiu F, et al. Randomized comparative trial and cost analysis of three-day antimicrobial regimens for treatment of acute cystitis in women. *JAMA* 1995;273:41-45.
106. Hooton TM, et al.Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. *JAMA* 1995;273:41-5.
107. Dimateo MR. Patient adherence to pharmacotherapy: The importance of effective communication. *Formulary* 1995;30:596-605.
108. Katz BP, Zwickl BW, Compliance with antibiotic therapy for *Chlamydia trachomatis* and *Neisseria gonorrheae*. *Sex Trans Dis* 1992;6:351-4.
109. McCormack WM: Pelvic inflammatory disease. *N Eng J Med* 1994;330:115-119.
110. Therapy for Sexually Transmitted Diseases. *Med Lett* 1994;913: 1-4.
111. Ambulatory PID Research Group. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. *South Med J* 1993;6:604-610.
112. Soper DE, Brockwell NJ, Dalton HP. Microbial etiology of urban emergency department acute salpingitis: Treatment with ofloxacin, *Am J Obstet Gynecol* 1992;3:653-60.
113. Sweet RL. Pelvic inflammatory disease. *Hosp Pract* 1993;28 (suppl 2):25-30.
114. Rolle C. *(Tuscon Medical Center, personal communication)*
115. Evaluation of new anti-infective agents for the treatment of acute pelvic inflammatory disease. *Clin Infect Dis* 1992;15 (suppl): S33-42.
116. Witkin SS, Ledger WJ. New directions in diagnosis and treatment of pelvic inflammatory disease. *J Antimicrob Chemother* 1994;2:197-199.

Physician CME Questions

97. Which single antibiotic provides a reasonable monotherapeutic, empiric option in older patients who are suspected of having a gram-negative, non-pseudomonas organism (i.e., *E. coli* or *klebsiella*) as a possible offender in their community-acquired pneumonia?
    A. Clarithromycin
    B. Erythromycin
    C. Levofloxacin
    D. Azithromycin
    E. None of the above.

98. Increasing resistance to which of the following organisms causing community-acquired pneumonia has become an issue of concern to ED physicians?
   A. B-hemolytic streptococcus
   B. *Streptococcus viridans*
   C. *Streptococcus pneumoniae*
   D. *E. coli* sp.
   E. None of the above

99. Which of the following antibiotic is approved for single course therapy for uncomplicated UTI?
   A. Macrovantin
   B. Azithromycin
   C. Fosfomycin
   D. Levofloxacin
   E. None of the above

100. Azithromycin is approved for community-acquired pneumonia caused by:
   A. *Streptococcus pneumoniae.*
   B. *Hemophilus influenzae.*
   C. *Moraxella catarrhalis.*
   D. *Mycoplasma pneumoniae.*
   E. All of the above

101. The most common isolated bacterial pathogens in children with acute otitis media are:
   A. *Streptococcus pneumoniae.*
   B. *H. influenzae.*
   C. *M. catarrhalis.*

Emergency Medicine Reports' Clinical Updates Conference

January 22-24, 1997
The Ritz Carlton
Cancun, Mexico

Join Editor-in-Chief Gideon Bosker, MD, FACEP, members of the editorial board of *Emergency Medicine Reports*, and the nation's leading experts on emergency medicine for a fast-paced, three-day, interactive seminar. Topics include: fever, infectious disease, and occult bacteremia emergencies; stroke management; diagnositic challenges with abdominal pain; and preventing the missed MI. In addition, participants will have the opportunity to earn 11.25 CME credit hours. Space is limited, so make your reservation today.

For fastest service, register by phone using VISA, MasterCard, Discover, or American Express: 1-800-688-2421.

102. The shortest approved antibiotic treatment course for acute otitis media is five days of therapy with the following suspension:
   A. clarithromycin.
   B. loracarbef.
   C. trimethoprim/sulfamethoxazole.
   D. azithromycin.
   E. fosfomycin.

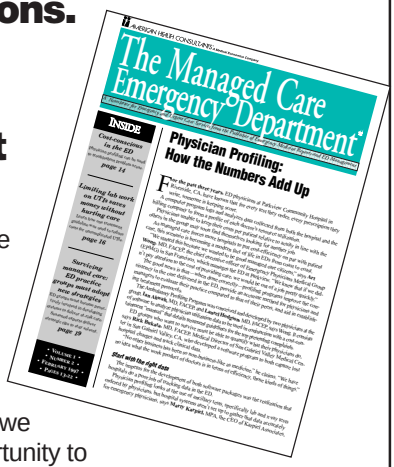
103. Which of the following is *not* approved for single-dose therapy for uncomplicated gonorrhea?
   A. Cefixime
   B. Azithromycin
   C. Clarithromycin
   D. Ciprofloxacin
   E. Norfloxacin

104. Which of the following regimens offers the shortest (i.e., 7 day) total treatment course for pelvic inflammatory disease?
   A. Ceftriaxone plus doxycycline
   B. Ceftriaxone plus tetracycline
   C. Azithromycin IV/oral sequenced combination regimen
   D. Cefotetan plus metronidazole
   E. None of the above

In Future Issues

Conscious Sedation

Preauthorizations. Cost Containment. MCO Contract Strategies.



These are just a few of the concepts faced by clinicians and managers in the modern ED. In recognition of your continued support of *Emergency Medicine Reports,* we are offering you the opportunity to receive the monthly newsletter ***The Managed Care Emergency Department*** at substantial savings and with absolutely no risk!

Each issue of ***The Managed Care Emergency Department*** offers in-depth articles about EDs and emergency physicians across the country who are coping with managed care, the latest news on new legislation, strategies for contracting, and practicing cost-effective medicine.

Subscribe now to receive **20 free hours** of AMA Category 1 CME. As always, you'll remain protected by our unconditional money-back guarantee for the life of your subscription.

For fastest service, call 1-800-688-2421.