Journal: **Clinics in chest medicine**

Date: **Jun 1991**
Vol: **12 (2)** Pgs: **395-407**

Article
Title: Oral antibiotics for pneumonia.

Author: Hampson NB

Imprint:

Call #: M00219620K

Location: LSC

Item #: 2

DATE: Thursday, April 02, 2015

Neil Hampson (neil.hampson@vmmc.org)
42306 N Caledonia Way
Anthem, AZ

Phone: **206-817-9945**

UHMS

0272–5231/91 $0.00 + .20

Oral Antibiotics for Pneumonia

Neil B. Hampson, MD, Roger A. Woolf, PharmD,† and Steven C. Springmeyer, MD‡*

Pneumonia is a significant cause of morbidity and death in the United States, affecting more than 3 million Americans each year and necessitating the hospitalization of more than 500,000 annually.[76] Community-acquired pneumonia requiring hospitalization may have a mortality rate of 10% to 25%,[46] emphasizing the importance of prompt and effective treatment. As the majority of patients are not hospitalized, a thorough understanding of oral antibiotic selection for the initial treatment of pneumonia is essential. This includes a knowledge of the antibiotic classes available for oral administration, the utility of diagnostic testing to determine an etiologic agent, the epidemiology of causative agents in pneumonia, the antibiotic sensitivities of those organisms, and, finally, a rational approach to empiric therapy when the infectious agent cannot be immediately identified. This article will review these topics with the goal of improved therapeutic efficacy in the oral treatment of pneumonia.

CLASSES OF ORAL ANTIBIOTICS

Numerous agents are available for the treatment of pulmonary infections. Appropriate use requires an understanding of their spectrum of activity, pharmacology, adverse effects, and expense profile. The classes of antibiotics described here represent those available in an oral dosage form that can be used in the primary treatment of mild to moderate pulmonary infections or the continuation of therapy that was initiated parenterally.

Penicillins

Mechanism of Action and Resistance. The antibacterial activity of penicillins results from the inhibition of cell wall synthesis. This inhibition is accomplished by covalent binding to various penicillin-binding proteins (PBPs) involved in the mucopeptide synthesis of the bacterial cell wall. The primary mechanism of resistance to penicillins is the production of β-lactamases, which hydrolyze the β-lactam structure of the penicillins and thereby inactivate the drug. Altered PBPs with decreased affinity for penicillin or a reduction in the outer membrane permeability of gram-negative organisms can contribute to penicillin resistance.[41, 53]

Spectrum of Activity. The penicillins remain an important class of antibiotics for the treatment of pulmonary infections. The various agents can be conveniently divided into classes based on antibacterial activity.[41, 49, 53]

The natural penicillins, penicillin G and penicillin V, are active against several respiratory pathogens, including the most common, *Streptococcus pneumoniae*. Penicillin-resistant *Strep. pneumoniae* has only rarely been encountered.[20] Most oropharyngeal anaerobes (except *Bacteroides fragilis*) are inhibited by penicillin. Penicillins G and V are readily hydrolyzed by β-lactamases and therefore are not effective against β-lactamase–producing strains of staphylococci and *Haemophilus influenzae*. Most gram-negative organisms are resistant to penicillin because of either outer cell-membrane impermeability or the production of β-lactamases.

*Staff Physician, Section of Pulmonary and Critical Care Medicine, Virginia Mason Clinic; and Clinical Instructor, Department of Medicine, University of Washington, Seattle, Washington
†Clinical Coordinator, Pharmacy Services, Virginia Mason Medical Center, Seattle, Washington
‡Staff Physician, Section of Pulmonary and Critical Care Medicine, Virginia Mason Clinic; and Associate Clinical Professor of Medicine, Department of Medicine, University of Washington, Seattle, Washington

Table 1. *Pharmacokinetic Properties of Oral Antibiotics*

GENERIC NAME	ORAL ABSORPTION (%)	FOOD DECREASES ABSORPTION	PEAK SERUM LEVEL (μg/ml) (DOSE)*	PROTEIN BINDING (%)	SERUM HALF-LIFE (HRS)	MAJOR ROUTE OF EXCRETION
Penicillins						
Penicillin G	20	Yes	2 (500 mg)	55	0.5	Renal
Penicillin V	60	No	4 (500 mg)	80	1	Renal
Ampicillin	40	Yes	3.5 (500 mg)	17	1	Renal
Amoxicillin	75	No	7.5 (500 mg)	17	1	Renal
Cloxacillin	50	Yes	10 (500 mg)	94	0.5	Renal
Dicloxacillin	50	Yes	15 (500 mg)	97	0.5	Renal
Amoxicillin/clavulanic acid‡	75	No	7.1/3.1 (500/125 mg)	20/30	1/1	Renal
Cephalosporins						
Cephradine	95	No	21.3 (15 mg/kg)	6–15	0.7	Renal
Cephalexin	95	No	23.4 (15 mg/kg)	6–20	0.75	Renal
Cefadroxil	95	No	13.7 (15 mg/kg)	20	1.2	Renal
Cefaclor	95	No	13.1 (15 mg/kg)	25	0.8	Renal
Cefuroxime	37–52	Increases	13.6 (15 mg/kg)	33–50	1.3	Renal
Cefixime	40	No	4.8 (400 mg)	67	3	Renal
Erythromycin						
Erythromycin base	n/a	Yes	0.3–1.9 (500 mg)	40–90	1.4	Biliary
Erythromycin stearate	n/a	Yes	0.4–1.8 (500 mg)	40–90	1.4	Biliary
Erythromycin estolate	n/a	No	1.1 (500 mg)†	40–90	1.4	Biliary
Erythromycin ethylsuccinate	n/a	Yes	0.6 (500 mg)†	40–90	1.4	Biliary
Miscellaneous						
Tetracycline	77	Yes	4 (500 mg)	65	8	Renal
Doxycycline	93	No	2.5 (200 mg)	93	18	Renal/fecal
Trimethoprim/sulfamethoxazole‡	85–90	No	2/40 (100 mg/80 mg)	65–70/70	10/11	Renal
Clindamycin	90	No	2.5 (150 mg)	90	2.4	Biliary
Ciprofloxacin	85	No	2.3 (500 mg)	35	3.4	Renal/biliary

*Peak levels based on single dose in fasting state.
†Represents free base level.
‡Parameters listed for both drug components.
Adapted from references 3, 14, 41, 53, 55 and 66.

The penicillinase-resistant penicillins with adequate absorption after oral administration are cloxacillin and dicloxacillin. This group of penicillins is resistant to hydrolysis by β-lactamases produced by *Staphylococcus aureus*. They are considered the drug of choice for most infections caused by *Staph. aureus*, despite the increasing incidence of methicillin-resistant strains.

The extended-spectrum penicillins include ampicillin and the related compounds amoxicillin, bacampicillin, and cyclacillin. They are very similar to penicillin G in their spectrum of activity but are more active against certain gram-negative organisms, including β-lactamase–negative *H. influenzae* and *Moraxella (Branhamella) catarrhalis*, many *Escherichia coli*, and some *Proteus mirabilis*. This increased activity is secondary to enhanced penetration through the outer membrane of gram-negative bacteria. These agents are susceptible to β-lactamases and therefore are not active against staphylococci or gram-negative organisms that produce β-lactamases.

The common occurrence of β-lactamases that mediate resistance to β-lactam antibiotics has led to the development of β-lactamase inhibitors. The inhibitor clavulanic acid is available as an oral combination preparation with amoxicillin. The clavulanic acid component extends the spectrum of amoxicillin activity to include β-lactamase–producing strains of *Staph. aureus*, *H. influenzae*, and *M. catarrhalis* and several aerobic and anaerobic gram-negative bacilli such as *Klebsiella pneumoniae* and *Bacteroides fragilis*.

Of the antipseudomonal penicillins, only carbenicillin is available in an oral dosage form. It achieves therapeutic levels only in the urine and therefore should not be considered for the treatment of pulmonary infections.

Pharmacology. Penicillins differ significantly in the extent of absorption after oral administration (Table 1).[41, 53] Penicillin G is unstable to acid and is not well absorbed from the gastrointestinal tract. Penicillin V is more extensively and reliably absorbed and therefore the preferred agent for oral therapy.

Ampicillin is only about 40% absorbed, whereas amoxicillin is almost completely absorbed, with peak levels 1.5 to 2 times those provided by the same dose of ampicillin. This better absorption permits less frequent dosing (every 8 hours), and less drug remains in the gastrointestinal tract to produce diarrhea. Bacampicillin and cyclacillin are essentially pro-

Table 2. *Dosing and Expense Profile of Oral Antibiotics*

GENERIC NAME	TRADE NAME	ADULT DOSE (mg) AND INTERVAL (hr)	GENERIC AVAILABLE	COST PER 10 DAYS THERAPY*
Penicillins				
Penicillin V	Veetids, Pen VK	250–500 q6	Yes	2.50
Ampicillin	Principin, Omnipen	250–500 q6	Yes	4.50
Amoxicillin	Amoxil, Polymox	250–500 q8	Yes	4.50
Cloxacillin	Cloxapen, Tegopen	250–500 q6	Yes	17.50
Dicloxacillin	Dynapen, Pathocil	250 q6	Yes	13.00
Amoxicillin/clavulanic acid	Augmentin	250–500 q8†	No	42.00
Cephalosporins				
Cephradine	Velocef, Anspor	250–500 q6	Yes	24.50
Cephalexin	Keflex, Keftab	250–500 q6	Yes	22.50
Cefadroxil	Duricef, Ultracef	500 q12	Yes	39.00
Cefaclor	Ceclor	250–500 q8	No	57.00
Cefuroxime	Ceftin	250–500 q12	No	57.50
Cefixime	Suprax	200 q12	No	41.50
Erythromycin				
Erythromycin base	E-mycin, Ery-tab	250–500 q6	Yes	7.50
Erythromycin estolate	Ilosone	250–500 q6	Yes	8.50
Erythromycin stearate	Erythrocin	250–500 q6	Yes	7.50
Erythromycin ethylsuccinate	E.E.S.	400–800 q6	Yes	12.00
Miscellaneous				
Tetracycline	Achromycin	250–500 q6	Yes	2.00
Doxycycline	Vibramycin	50–100 q12	Yes	3.00
Trimethoprim-sulfamethoxazole	Bactrim, Septra	80–160 q12‡	Yes	3.00
Clindamycin	Cleocin	150–300 q6	Yes	34.00
Ciprofloxacin	Cipro	250–500 q12	No	39.50

*Cost to the pharmacist for 10 days' treatment based on Average Wholesale Price Listing in *Drug Topics Red Book 1989*. Reflects average price for generic when available.
†Dosage of amoxicillin component.
‡Dosage of trimethoprim component.
Data from references 10 and 55.

drugs of ampicillin designed to improve overall absorption. They have no therapeutic advantage over amoxicillin and tend to be substantially more costly.

Of the penicillinase-resistant penicillins, only cloxacillin and dicloxacillin produce high and predictable blood levels with oral administration.

Penicillins are well distributed into most body fluids, including the lung and pleural space. Their route of elimination is the kidney, both by glomerular filtration and by tubular secretion.

Adverse Effects. Allergic reactions are the best known side effects of the penicillins and range in severity from a rash to immediate anaphylaxis. Gastrointestinal disturbance can follow the use of any of the oral penicillins but is most pronounced with ampicillin and higher dosages of the amoxicillin-clavulanic acid combination.

Cephalosporins

Mechanisms of Action and Resistance. Numerous cephalosporins have appeared over the past decade, with more than 20 agents currently on the US market and six available in an oral dosage form. Cephalosporins are β-lactam antibiotics like the penicillins with essentially the same mechanisms of antibacterial activity and resistance.

Spectrum of Activity. On the basis of differences in activity, the cephalosporins have traditionally been classified into generations.[14, 41, 66] Progression from the first to the third generation generally means a greater resistance to β-lactamase, a broader gram-negative spectrum, and higher cost (Table 2).

The first-generation cephalosporins, cephalexin, cephradine and cefadroxil, have similar activity and can be considered therapeutically interchangeable. They have a broad spectrum of activity against several pulmonary pathogens, including most streptococci, staphylococci, and a limited number of community-acquired gram-negative organisms.

The second-generation cephalosporins include cefaclor and cefuroxime axetil. They have increased β-lactamase stability and somewhat broader activity against gram-negative organ-

isms. Of particular note in pulmonary infections is the increased activity against β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.

The oral third-generation cephalosporin, cefixime, is significantly more active than the other cephalosporins against gram-negative organisms including *E. coli*, *K. pneumoniae*, *P. mirabilis*, and β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.[52] Cefixime is highly active against *Strep. pneumoniae* but, unlike the other cephalosporins, is not very active against *Staph. aureus*.

Pharmacology. The pharmacologic features of the oral cephalosporins are shown in Table 1.[14, 66] In general, these agents are rapidly and well absorbed. Cephradine, cephalexin, cefadroxil, and cefaclor are almost completely absorbed, with cefuroxime and cefixime being absorbed to a lesser extent. Cephradine, cefadroxil, and cefaclor achieve higher peak serum concentrations when taken on an empty stomach. Cefixime absorption is unaffected by food, and cefuroxime has better absorption when taken with food.[66] With the exception of cefixime, all of the oral cephalosporins are eliminated unchanged in the urine. Cefixime is eliminated primarily by nonrenal mechanisms such as the biliary tract.

Cefadroxil and cefuroxime have longer half-lives, which allows 12-hour dosing as opposed to 6- to 8-hour dosing for cephradine, cephalexin, and cefaclor. Cefixime has the longest half-life (3 to 4 hours) and may be given once or twice daily.

Adverse Effects. Hypersensitivity reactions and gastrointestinal upset are the most common adverse effects associated with oral cephalosporins. The rate of cross allergy to cephalosporins in penicillin-allergic patients ranges from 5% to 16%.[14] Use of cephalosporins in penicillin-allergic patients should be guided by the severity of the allergic reaction and the availability of treatment alternatives. Thus, every effort should be made to avoid cephalosporins in patients who have had immediate IgE-mediated reactions (e.g., anaphylaxis), but it is reasonable to consider cephalosporin use in patients with a history of less serious allergic reactions.

Erythromycin

Mechanism of Action and Resistance. Erythromycin is a bacteriostatic agent that exerts its effect by interfering with protein synthesis at the 50S ribosomal subunit. Resistance usually involves alterations in this subunit that decrease the binding of the drug.

Spectrum of Activity. Erythromycin is a macrolide antibiotic with activity against gram-positive cocci including *Strep. pneumoniae* and group A streptococci, some *H. influenzae*, most anaerobes, and miscellaneous organisms including *Mycoplasma pneumoniae*, atypical mycobacteria, *Legionella pneumoniae*, and some rickettsiae.[68, 74] With regard to pulmonary infections, its principal clinical use is as an alternative to penicillin for pneumococcal pneumonia and as a primary drug of choice for mycoplasma infection and Legionnaires' disease.

Pharmacology. Erythromycin base and its available salts (stearate, estolate, and ethylsuccinate) are well absorbed in the fasting state. The base and stearate salt are absorbed as the free base, whereas the estolate and ethylsuccinate are absorbed as both intact ester and free base. When comparing the bioavailability of the various dosage forms, one must distinguish between the serum levels of the active base and of the inactive esters. Estolate products produce total serum levels (base plus ester) that are approximately three times those achieved with the base or stearate. However, free base levels achieved with estolate administration are similar to those achieved with the other forms, as only 20% to 30% of the total level is present as free base. Only about 55% of the ethylsuccinate preparation is absorbed as free base, necessitating administration of 400 mg of ethylsuccinate to produce free erythromycin serum levels equivalent to those seen with 250 mg of the other dosage forms. In general, the erythromycin preparations have various degrees of bioavailability but produce similar free base levels when taken in the fasting state (see Table 1).[68] Food in the stomach reduces absorption except with the estolate and some enteric-coated base formulations. Erythromycin diffuses readily and results in therapeutic concentrations in pulmonary secretions and tissue.[68] Most of the drug is concentrated in the liver and excreted into the bile. Less than 5% appears in the urine as unchanged drug.

Adverse Effects. Gastrointestinal distress is the most common side effect of oral therapy. This effect appears to be secondary to stimulation of gastrointestinal motility by erythromycin and tends to be dose related. Symptoms may be lessened by taking the medication with food or by temporarily reducing the dose. There are no adequate data in adults to indicate that any formulation of erythromycin produces fewer

gastrointestinal side effects. Cholestatic hepatitis has occurred rarely with erythyromycin administration, most commonly with the estolate preparation.[74] In view of the bioavailability, adverse effects, and cost, enteric-coated base should be considered the product of choice for most situations.

Erythromycin can reduce the clearance of certain drugs (theophylline, warfarin, carbamazepine, and others) by inhibiting hepatic metabolism. Patients receiving concomitant therapy should be monitored for evidence of toxicity.

Tetracyclines

Mechanism of Action and Resistance. The tetracyclines are bacteriostatic and exert their effect by binding to the 30S subunit of the bacterial ribosome to inhibit protein synthesis. Resistance is mediated by reduced transport of tetracycline into the cell or by an increase in the organism's ability to export the drug out of the cell.[67]

Spectrum of Activity. In general, all tetracycline analogues have a similar spectrum of activity, and none possesses a therapeutic advantage over tetracycline. Tetracyclines are broad-spectrum agents with activity similar to that of erythromycin against bacteria, mycoplasmas, chlamydiae, and rickettsiae. Tetracyclines have greater activity against gram-negative organisms, but widespread indiscriminate use has resulted in extensive bacterial resistance.[67]

Pharmacology. Although several tetracycline derivatives are available, only tetracycline and doxycycline need be considered for therapy of pulmonary infections. Oral absorption generally exceeds 80% but can be significantly poorer in the presence of food or polyvalent cations such as iron, aluminum salts, and milk products containing calcium. All tetracyclines are excreted in the urine and feces. Tetracycline is primarily excreted by the kidneys by glomerular filtration. Doxycycline is excreted with a greater extent in the feces as an inactive conjugate and does not accumulate in renal failure.[67]

Adverse Effects. Gastrointestinal upset, diarrhea, and photosensitivity are the most common adverse effects. Tetracyclines should not be used in children or pregnant women because of deposition in the bones and teeth.

Clindamycin

Mechanism of Action and Resistance. Clindamycin acts at the level of the 50S ribosome to inhibit protein synthesis. Resistance is most likely the result of alteration of the ribosome that interferes with antibiotic binding.

Spectrum of Activity. Clindamycin is active against most staphylococci and streptococci and broadly active against both gram-positive and gram-negative anaerobes, including *B. fragilis*. With regard to pulmonary infections, the primary use is in the treatment of lung abscess and aspiration pneumonia.[68]

Pharmacology. Clindamycin is well absorbed (90%) after oral administration. Absorption is slightly delayed but not decreased by ingestion of food. Most of the drug is metabolized and excreted in the bile.

Adverse Effects. Hypersensitivity reactions can occur, but the most common side effects involve the gastrointestinal tract. Effects range from upset to pseudomembranous colitis secondary to toxin produced by an overgrowth of *Clostridium difficile*.

Trimethoprim-Sulfamethoxazole

Mechanism of Action and Resistance. Sulfamethoxazole and trimethoprim inhibit different enzymes in the bacterial folic acid synthesis pathway. Resistance is most often attributable to acquisition of alternative enzymes.[42]

Spectrum of Activity. The combination has activity against both gram-positive and gram-negative organisms, including many strains of *Staph. aureus, H. influenzae, E. coli, P. mirabilis,* and *Klebsiella* species.

Pharmacology. Trimethoprim is available for oral use in a fixed combination with sulfamethoxazole in a ratio of 1:5. Both trimethoprim and sulfamethoxazole are well absorbed and distribute widely into tissues, with lung and sputum levels being at least 80% of those in the plasma.[42] Both agents are partially metabolized and then excreted, primarily in the kidneys by glomerular filtration.

Adverse Effects. The common adverse effects of trimethoprim-sulfamethoxazole are nausea, diarrhea, rash, and drug fever. Serious adverse effects from the sulfa component include hemolytic anemia, hematopoietic depression, and hypersensitivity reactions, including Stevens-Johnson syndrome.

Quinolones

Nalidixic acid and cinoxacin are older quinolones used to treat urinary tract infections. The

new quinolones, although structurally related, have a much enhanced spectrum of activity and achieve good systemic levels after oral use. Ciprofloxacin is currently the only oral quinolone available with absorption adequate for the treatment of pulmonary infections. However, several other agents, including enoxacin, pefloxacin, and ofloxacin, are currently in clinical trials.

Mechanism of Action and Resistance. Quinolones exert their antibacterial effect by inhibiting an enzyme essential for DNA synthesis. This enzyme, DNA gyrase, is required for the supercoiling and relaxing of DNA strands during synthesis. Resistance is uncommon and occurs as a result of a mutation in DNA gyrase that reduces quinolone affinity.

Spectrum of Activity. In general, the quinolones have excellent activity against gram-negative pulmonary pathogens such as *H. influenzae* and the enterobacteriaceae. They also have good activity against *Pseudomonas aeruginosa* and staphylococci (including methicillin-resistant strains). Streptococci are somewhat less susceptible, and antianaerobe activity is poor. *Legionella* is also inhibited by the quinolones, and there is variable activity against mycoplasmas and chlamydiae.

Pharmacology. Ciproflaxacin is rapidly absorbed from the gastrointestinal tract and widely distributed in body fluids, with sputum levels equal to or exceeding the corresponding serum levels.[3] The absorption of all quinolones is significantly reduced by magnesium- or aluminum-containing antacids, and concomitant administration should be avoided.[59] Excretion is predominantly via the kidneys as unchanged drug. The serum half-lives of the fluoroquinolones generally are long, ranging from 4 hours for ciprofloxacin to 6 to 10 hours for some agents soon to be released. The long half-lives permit administration twice daily for ciprofloxacin and possibly once daily for some of the newer agents.

Adverse Effects. Gastrointestinal side effects are the most common adverse effect. Central nervous system side effects include headache, insomnia, and dizziness. Ciprofloxacin can inhibit the metabolism of theophylline and possibly increase the risk for theophylline toxicity.

IDENTIFICATION OF AN ETIOLOGIC AGENT FOR PNEUMONIA

When a patient presents with community-acquired lower respiratory-tract infection, several factors must be considered before selecting an oral antibiotic for treatment. First and foremost, the patient must be a candidate for treatment by the oral route. The clinician must not have a significant suspicion that the patient is likely to fail enteral administration of medication, because such failure may be associated with significant morbidity and even death. A candidate for treatment of bacterial pneumonia with an oral regimen should have limited disease, should be relatively nontoxic without bacteremia, should not have significant immunocompromise, and should be suspected to be infected by an organism generally sensitive to an oral regimen. Patients not meeting these criteria require hospitalization for initial parenteral antibiotic therapy and are not the focus of this discussion.

Primary clinical evaluation should attempt prompt identification of a specific microbe prior to selection of an antibiotic. The combination of clinical history, physical examination, chest radiograph, sputum examination, and blood culture frequently is sufficient to identify the infecting organism or to eliminate from consideration those patients who are not candidates for oral therapy.

Sputum analysis is the traditional first step toward specific identification of an etiologic agent for pneumonia. Sputum Gram stain has the potential to provide rapid recognition of a predominant organism. Because sputum originating in the lower respiratory tract may become contaminated with resident flora of the upper respiratory tract during expectoration, it is necessary to screen specimens to reduce the rate of false-positive tests. It has been suggested that sputum examined under low magnification ($\times 10$ objective) should exhibit fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per field to minimize the likelihood that the results represent contamination from the upper airway.[50] When this or similar screening has been performed, the finding of a predominant population of intracellular organisms correlates well with specimens obtained from the lower respiratory tract, allowing very specific antibiotic selection.[24, 50, 72]

Routine sputum culture has limitations similar to those of the sputum stain because of the potential for contamination by oral flora. Sputum culture results must be interpreted in light of the information previously gained by microscopic examination in an attempt to recognize the predominant pathogen among several that may be cultured.[29] The sensitivity of the sputum culture in proved pneumococcal pneumonia

ranges from 48% to 100%.[7, 21] Low diagnostic yield in community-acquired pneumonia of all etiologies occurs because sputum quality is poor, the pathogen is overgrown by colonizers or contaminants, and the organism may require specific culture media. Some investigators suggest that culture adds little to microscopic sputum examination when a predominant organism is seen on a good-quality specimen.[5, 38]

Blood culture has a sensitivity from 4% to 41% for diagnosis of community-acquired pneumonia.[8, 70, 75] Review of available studies would suggest an average yield of approximately 15%.[15, 38, 40] Despite this, two blood cultures should be obtained during the initial evaluation because isolation of a microorganism almost always correlates with the pulmonic infection and leads to very specific antimicrobial therapy. In addition, positive blood cultures identify patients who should receive parenteral therapy initially, as noted previously.

Early identification of a pathogen allows specific selection of antibiotic therapy. However, when the patient has clinical evidence of pneumonia and no predominant organism on Gram stain, oral antibiotic selection must be based at least in part on an epidemiologic knowledge of the disease. Many studies have been published over the past two decades that help shape the selection of empiric therapy. Eight of these studies are summarized in Table 3.[8, 31, 33, 38, 40, 45, 75, 78] Differences in the frequency of isolation of various organisms among these studies are attributable to differences among study populations, severity of illness, and diagnostic techniques. Despite this, general conclusions can be drawn regarding the incidence of various pathogens in acute lower respiratory tract infection. Additionally, it can be seen that even when specialized cultures and serology for both typical and atypical organisms are performed, no etiology is determined for as many as one half of the community-acquired pneumonias.

After a discussion of specific oral antibiotic treatment for the more common lower respiratory tract pathogens, an empiric approach to therapy will be outlined that is based on clinical factors and these epidemiologic data.

THERAPY FOR SPECIFIC ORGANISMS

Streptococcus pneumoniae

Streptococcus pneumoniae (pneumococcus) is the most frequent bacterial cause of community-acquired pneumonia in virtually all studies reported. Among those series summarized in Table 3, it was isolated in 9% to 76% of patients. When examination of a high-quality sputum specimen reveals a preponderance of gram-positive lancet-shaped diplococci, the presence of pneumococcus is strongly suggested. *Streptococcus pneumoniae* will usually grow from subsequent culture, and the patient responds to specific antipneumococcal therapy.[9, 61] Problems with the sensitivity of sputum analysis have previously been discussed.

In young adults with mild, uncomplicated pneumococcal pneumonia, oral antibiotics may be appropriate, and a number of agents are effective. Penicillin V is the drug of choice and will usually be effective in relatively low doses (250–500 mg four times daily). In cases of penicillin allergy, erythromycin may be substituted (500 mg four times daily). Alternatives such as first-generation cephalosporins, clindamycin, trimethoprim-sulfamethoxazole, tetracycline, and amoxicillin-clavulanic acid all possess activity against *Strep. pneumoniae* but are less acceptable than penicillin for reasons of cost, side effects, or effectiveness.

Use of the fluoroquinolone antibiotics for infections caused by *Strep. pneumoniae* has been a topic of debate. Ciprofloxacin is the most widely used fluoroquinolone in the United States. Concern has been raised because it has demonstrated high minimum inhibitory concen-

Table 3. *Etiology of Community-acquired Pneumonia (Per Cent)*

ORGANISM	BERNTSSON ET AL[8]	HOLMBERG[31]	KERTTULA ET AL[33]	LEVY ET AL[38]	MACFARLANE ET AL[40]	MARRIE ET AL[45]	WHITE ET AL[75]	WOODHEAD ET AL[78]
Strep. pneumoniae	54	47	25	26	76	9	11	36
H. influenzae	4	9	4	12	3	6	2	10
Mycoplasma pneumoniae	14	5	2	3	2	3	14	1
Legionella species	1	3		4	15	4	1	1
Oral anaerobes				3		11		
Chlamydia species	2	1	9	1	6	6	1	1
M. catarrhalis		2	6	1		1		
Coxiella burnetii			1		1	2	3	
Gram-negative bacilli				7	1	2	1	1
Staph. aureus	1	1		3	2	5	4	1
No etiology identified	21	29	51	35	3	37	51	45

trations (MICs) against the pneumococcus in preclinical in vitro studies.[64] In clinical trials, however, ciprofloxacin has been effective against *Strep. pneumoniae* lower respiratory tract infections,[4, 17, 36, 77] curing 23 of 25 patients with pneumococcal pneumonia in the largest such series reported.[36] Clinical effectiveness better than that expected from serum MIC data may be secondary to ciprofloxacin's high volume of distribution, with pulmonary tissue levels sometimes exceeding serum levels for significant periods of time.[32] Nonetheless, penicillin V remains the oral antibiotic of choice for lower respiratory infections known to be caused by *Strep. pneumoniae* because of well-proved efficacy and cost. The potential use of ciprofloxacin for treatment of pneumonia when the pathogen is unknown is discussed in the subsequent section on empiric treatment of pneumonia.

Pneumonia caused by penicillin-resistant pneumococci has been reported, typically outside the US.[20, 56] Penicillin resistance can be either relative or high level, depending on the MIC of penicillin for the organism. Most strains are only relatively penicillin resistant and may respond to intravenous high-dose penicillin therapy.[56] Strains with high-level resistance may require an alternative antibiotic such as vancomycin. No oral antibiotics have been reported to be reliably effective in pneumonia caused by penicillin-resistant pneumococci. This should be taken into consideration when treating patients in a geographic locale with a high incidence of antibiotic-resistant strains or when the patient with proved *Streptococcus pneumoniae* pneumonia does not respond to what is usually appropriate antibiotic therapy.

Haemophilus influenzae

Haemophilus influenzae was isolated as a pathogen in 2% to 12% of patients with pneumonia in the epidemiologic studies reported in Table 3. It is most common among patients with chronic pulmonary disease, alcoholics, and the elderly but may cause pneumonia in healthy adults as well. Clinical and roentgenographic findings in *H. influenzae* pneumonia are indistinguishable from those of other bacterial pneumonias,[18, 30, 51] but a sputum Gram stain may be characteristic when it demonstrates large numbers of small gram-negative coccobacilli. Elderly patients or those with underlying disease should initially receive parenteral antimicrobial therapy, but initial oral antibiotic therapy may be appropriate in young, otherwise healthy adults. β-Lactamase production by *H. influenzae* has been reported since the 1970s[69] but remains relatively uncommon in isolates from adults with pneumonia. Unless the organism is known to produce β-lactamase or production is suspected because of community prevalence, amoxicillin is the oral antibiotic of first choice. Amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, cefaclor, cefuroxime axetil, ciprofloxacin, and tetracycline all have excellent activity against both ampicillin-sensitive and ampicillin-resistant strains of *H. influenzae* and are acceptable alternatives.

Mycoplasma pneumoniae

Mycoplasma pneumoniae pneumonia usually occurs in family outbreaks, primarily affecting children and young adults.[43] The organism has been reported to be the cause of as many as 14% of community-acquired pneumonias in recently reported series (Table 3), and in some populations, it may be the cause of as many as 20% of all pneumonias and as many as 50% of pneumonias occurring in the summer.[22] Many infected individuals are asymptomatic or have upper respiratory infection without pneumonia. In patients with pneumonia, a sputum Gram stain reveals mononuclear and polymorphonuclear cells without a predominant organism, and sputum culture grows normal respiratory flora. Cold agglutinins are elevated in as many as 50% of cases.[43] In practice, the diagnosis of *Mycoplasma pneumoniae* pneumonia is generally made on clinical grounds. The illness is of insidious onset, generally benign in course, and frequently self-limited,[11, 22] although severe cases may occur.[39] In the typical case, initial outpatient treatment with oral antibiotics is appropriate.

As the organism lacks a cell wall, treatment with β-lactam antibiotics is ineffective. The organism is sensitive to both erythromycin and tetracycline. Treatment with either has been associated with a shorter duration of respiratory symptoms in patients with pneumonia than in those who receive no therapy or treatment with penicillin.[22] Appropriate antibiotic treatment does not, however, affect the antibody response or extrapulmonary complications.[11, 22] Recommended regimens of erythromycin or tetracycline are a total of 1.5 to 2.0 gm/day administered for 14 to 21 days. This organism is discussed more extensively elsewhere in this issue.

Legionella Species

Legionella pneumonia is an inhalational pneumonia caused by infection with members of the Legionellaceae family and accounting for 1% to 15% of cases of community-acquired pneumonia in recent series (Table 3). More than 25 species have been classified into the Legionellaceae family, 18 of which have been implicated in human pneumonias.[19] More than 90% of cases of community-acquired *Legionella* pneumonia are caused by *Legionella pneumophila*,[48] the agent responsible for the 1976 epidemic of Legionnaires' disease in Philadelphia.[23] In that epidemic, 23 different antibiotics were used to treat the patients.[71] Those treated with erythromycin or tetracycline were more likely to survive than those who received β-lactam antibiotics or aminoglycosides. Subsequent in vivo susceptibility testing has shown that erythromycin, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and the fluoroquinolones all afford protection against infection.[34, 63] All achieve high intracellular concentrations.

In clinical practice, *Legionella* pneumonia usually is treated initially with intravenous erythromycin, 500 to 1000 mg every 6 hours.[13, 34, 48] After clinical improvement is seen, the patient is switched to 500 mg orally every 6 hours for 3 weeks' total therapy. Rifampin (600 mg orally every 12 hours) is sometimes added for moderate or severe infections. The relative efficacy of alternatives to erythromycin is unclear, but the tetracyclines and trimethoprim-sulfamethoxazole have been suggested for use in erythromycin intolerance or failure.[13, 62] *Legionella* infections are discussed in detail elsewhere in this issue.

Anaerobic Infections

Anaerobic infections of the lung (abscess or pneumonia) typically are caused by mixed oral anaerobes and result from aspiration of a large quantity of oropharyngeal contents. The typical patient has abnormal swallowing or a history of altered consciousness and poor dentition. The sputum may be foul smelling, and the Gram stain typically demonstrates white cells with abundant organisms of many varieties. Penicillin V or clindamycin may be administered orally in appropriate mildly ill patients.[6] As the responsible bacteria may be mixed with aerobic organisms, including gram-negative bacilli, amoxicillin-clavulanic acid is an excellent agent as well.

Chlamydia Species

Two species of the *Chlamydia* genus cause pneumonia in immunocompetent adults: *Chlamydia psittaci* and *Chlamydia pneumoniae* strain TWAR. Psittacosis (parrot fever) is a zoonosis infrequently recognized in the US.[65] It is caused by infection with *Chlamydia psittaci*, the reservoir of which is infected birds. The oral treatment of choice is tetracycline (1–2 gm/day for 14 to 21 days), although erythromycin also is effective.[65]

Chlamydia pneumoniae strain TWAR has been more recently recognized as an etiology of adult pneumonia,[27] as discussed elsewhere in this issue. It has been reported as the causative agent of pneumonia in 12% of a series of college students and in 6% to 10% of adults with community-acquired pneumonia.[26, 27, 45] In vitro drug susceptibility testing of strain TWAR demonstrates that tetracycline and erythromycin are the most effective and that sulfa is not effective.[37] However, small doses or short courses of erythromycin have been associated with persistent respiratory symptoms or clinical relapse.[27] In a study of military recruits, high-titer IgG antibody developed after treatment of *Chlamydia pneumoniae* strain TWAR with ampicillin or penicillin, but antibody response was depressed or absent in patients treated with tetracycline.[35] Currently recommended therapy for infection with *Chlamydia pneumoniae* is tetracycline or erythromycin, 2 gm/day for 10 to 14 days.[25] Alternative therapy can be 1 gm/day for 21 days.

Moraxella (Branhamella) catarrhalis

Moraxella (Branhamella) catarrhalis (formerly *Neisseria catarrhalis*) has long been recognized as an organism common to the normal respiratory flora. More recently, the organism has been recognized as a lower respiratory tract pathogen.[73] Pulmonary infection caused by *M. catarrhalis* typically occurs in patients with underlying lung disease and usually manifests as acute tracheobronchitis or an exacerbation of chronic bronchitis, although pneumonia may occur.[28, 73, 79] *Moraxella catarrhalis* is identified as a pathogen in as many as 6% of cases of community-acquired pneumonia (Table 3). *Moraxella catarrhalis* pneumonia is frequently diagnosed from the sputum Gram stain, which shows large numbers of polymorphonuclear leukocytes and many large kidney bean-shaped gram-negative diplococci.[79] β-Lactamase may

be produced by as many as 86% of *M. catarrhalis* sputum isolates,[1, 2] and clinical resistance to ampicillin or amoxicillin has been demonstrated in patients infected with β-lactamase–producing strains.[47, 54] Because of the high prevalence of resistance, first-line therapy with these drugs or penicillin is not recommended. Effective oral antibiotics for both β-lactamase–positive and -negative strains include tetracycline, erythromycin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, ciprofloxacin, cefuroxime axetil, and cefixime.

Q Fever

Q fever pneumonia is a zoonosis caused by the rickettsial organism, *Coxiella burnetii*. This pleomorphic coccobacillus infects a wide range of animals and insects, with domestic livestock and cats serving as the reservoir for human disease. Q fever pneumonia has a variable clinical presentation, ranging from mild to severe and without characteristic features.[44] The illness may remit without antibiotic therapy, but tetracycline has been shown in a randomized study to reduce the duration of fever by 50% if administered early in the course of the illness.[60] A 2-week course of tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily) is considered the treatment of choice.[44] Success with erythromycin treatment has been reported,[12, 16] although other authors have had less success.[44] In vitro testing of *Coxiella burnetii* has demonstrated sensitivity to rifampin and ciprofloxacin,[80] and rifampin administration has produced a prompt response.[44]

Enteric Gram-Negative Bacilli and *Staphylococcus aureus*

Gram-negative bacillary pneumonia caused by the Enterobacteriaceae or *Pseudomonas aeruginosa* is rare among cases of community-acquired pneumonia (Table 3), occurring typically in the hospitalized patient, the institutionalized elderly, or in patients with serious underlying diseases. Because these infections are associated with a high mortality rate,[40, 70] hospitalization with initial parenteral antimicrobial therapy is indicated. Oral antibiotics may be used after the patient has stabilized and improved clinically and should be selected on the basis of MIC data of the clinical isolate. Ciprofloxacin frequently is an effective agent in this clinical setting because of its broad gram-negative spectrum.[57, 64]

Staphylococcus aureus pneumonia is also rare in healthy adults, with most cases occurring among institutionalized elderly, intravenous drug users, chronic hemodialysis patients, or diabetics or after primary influenza A infection. Patients are usually toxic and may exhibit an explosive clinical presentation.[76] Mortality rates may be significant,[40, 70] again warranting initial hospital admission for parenteral antibiotics. Subsequent selection of oral therapy will be based on the in vitro resistance of the strain. If it is methicillin sensitive, subsequent oral dicloxacillin is the treatment of choice. Erythromycin, clindamycin, ciprofloxacin, and amoxicillin-clavulanic acid may also be effective. Ciprofloxacin has good in vitro activity against methicillin-resistant strains of *Staph. aureus*[64] and in one study cured four of six patients with mild pneumonia caused by methicillin-resistant *Staph. aureus*.[58]

EMPIRIC SELECTION OF ORAL ANTIBIOTICS FOR PNEUMONIA

Initial antibiotic therapy for most patients with community-acquired pneumonia must be empiric, as the common types of the disease have few distinguishing clinical characteristics. If the initial evaluation does not reveal a definite cause, treatment should not be postponed while awaiting information from specific laboratory tests. Even when extensive sophisticated laboratory testing is performed, no etiology is determined for as many as half the cases of community-acquired pneumonia (Table 3). Empiric antibiotic selection must take into account the clinical presentation, epidemiologic data about the patient (such as age, underlying disease, residence), epidemiology of organisms responsible for community-acquired pneumonia (Table 3), and immediately available laboratory information such as the sputum Gram stain.

The type of clinical presentation can be very helpful in guiding antibiotic selection. Acute illness of sudden onset associated with purulent sputum, fever, and chills is likely to be caused by the usual bacteria. The sputum Gram stain may be diagnostic for infections with *Strep. pneumoniae, H. influenzae, M. catarrhalis,* oral anaerobes, *Staph. aureus*, or gram-negative bacilli. When oral antibiotic administration is appropriate, treatment can be selected as previously described for these organisms.

When the sputum Gram stain is nondiagnostic or the clinical presentation subacute, of gradual onset, and associated with little or no

sputum production, antibiotic selection is empiric and must include epidemiologic considerations. In the young, otherwise healthy adult, erythromycin is the treatment of choice, as it provides adequate coverage for infection with *Strep. pneumoniae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* strain TWAR. Mycoplasma infection is rare in the elderly, and empiric administration of penicillin V may be appropriate. The treatment spectrum can be expanded to include *H. influenzae* by instead administering amoxicillin or, in the case of β-lactamase–producing strains, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, or a cephalosporin. *Legionella* infection is rare in most communities but should be covered by erythromycin administration if such infection is prevalent. Patients with esophageal disease, neuromuscular disorders, alcoholism, or altered mental status are prone to aspiration and may be infected with mixed oral anaerobes. Empiric treatment with penicillin V, clindamycin, or amoxicillin-clavulanic acid is appropriate. Infections with *H. influenzae, Staph. aureus, M. catarrhalis,* and gram-negative bacilli are more prevalent among residents of nursing homes, patients with chronic bronchitis, and patients with a history of alcohol abuse. Empiric treatment with trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, or a second-generation cephalosporin is appropriate in this group. Failure to respond to therapy raises the question of infection with *Legionella* or other atypical organism, and erythromycin can be added to the regimen. Suspected bacterial pneumonia following an influenza infection should be treated with an agent such as dicloxacillin, although initial parenteral antibiotic therapy is advised if *Staph. aureus* infection is strongly suspected. In the patient with subacute pneumonia and history of exposure to birds or livestock, empiric treatment with tetracycline or doxycycline provides coverage for psittacosis and Q fever.

With regard to empiric administration of ciprofloxacin for treatment of community-acquired pneumonia, some authors have recommended its use in the elderly patient with relatively mild infection because of the increased incidence of gram-negative pathogens.[57] However, this group is also prone to aspiration and development of anaerobic infection. Ciprofloxacin has little activity against obligate anaerobes[64] and should be avoided if their presence is likely. Amoxicillin-clavulanic acid therefore may be a better choice in the elderly patient with mild infection because of its gram-negative and anaerobic coverage.

REFERENCES

1. Ahmad F, McLeod DT, Croughan MJ, et al: Antimicrobial susceptibility of *Branhamella catarrhalis* isolates from bronchopulmonary infections. Antimicrob Agents Chemother 26:424–425, 1984
2. Alvarez S, Jones M, Holtsclaw-Berk S, et al: In vitro susceptibilities and beta-lactamase production of 53 clinical isolates of *Branhamella catarrhalis*. Antimicrob Agents Chemother 27:646–647, 1985
3. Andriole VT: Quinolones. *In* Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases, ed 3. New York, Churchill Livingston, 1990, pp 334–345
4. Bantz PM, Grote J, Perts-Haertel W, et al: Low-dose ciprofloxacin in respiratory tract infections: A randomized comparison with doxycycline in general practice. Am J Med 82 (suppl 4A):208–210, 1987
5. Barrett-Connor E: The nonvalue of sputum culture in the diagnosis of pneumococcal pneumonia. Am Rev Respir Dis 103:845–848, 1971
6. Bartlett JG: Anaerobic bacterial infections of the lung. Chest 91:901–909, 1987
7. Bartlett JG, Finegold SM: Bacteriology of expectorated sputum with quantitative culture and wash technique compared to transtracheal aspirates. Am Rev Respir Dis 117:1019–1027, 1978
8. Berntsson E, Blomberg J, Lagergard T, et al: Etiology of community-acquired pneumonia in patients requiring hospitalization. Eur J Clin Microbiol 4:268–272, 1985
9. Boerner DF, Zwadyk P: The value of the sputum gram's stain in community-acquired pneumonia. JAMA 247:642–645, 1982
10. Cardinale VA, Thurlow RM (eds): Drug Topics Red Book. Oradell, NJ, Medical Economics Company, 1989
11. Cassell GH, Cole BC: Mycoplasmas as agents of human disease. N Engl J Med 304:80–89, 1981
12. D'Angelo LJ, Hetherington R: Q fever treated with erythromycin. Br Med J 2:305–306, 1979
13. Davis GS, Winn WC Jr: Legionnaires' disease: Respiratory infections caused by Legionnella bacteria. Clin Chest Med 8:419–439, 1987
14. Donowitz GR, Mandell GL: Cephalosporins. *In* Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases, ed 3. New York, Churchill Livingston, 1990, pp 246–257
15. Dorff GJ, Rytel MW, Farmer SG, et al: Etiologies and characteristic features of pneumonias in a municipal hospital. Am J Med Sci 266:349–358, 1973
16. Ellis ME, Dunbar EM: *In vivo* response of acute Q fever to erythromycin. Thorax 37:867–868, 1982
17. Ernst JA, Sy ER, Colon-Lucca HC, et al: Ciprofloxacin in the treatment of pneumonia. Antimicrob Agents Chemother 29:1088–1089, 1986
18. Everett ED, Rahm AE Jr, Adaniya R, et al: *Haemophilus influenzae* pneumonia in adults. JAMA 238:319–321, 1977
19. Fang GD, Yu VL, Vickers RM: Disease due to the Legionellaceae (other than *Legionella pneumophila*): Historical, microbiological, clinical, and epidemiological review. Medicine (Baltimore) 68:116–132, 1989

20. Feldman C, Kallenbach JM, Miller SD, et al: Community-acquired pneumonia due to penicillin-resistant pneumococci. N Engl J Med 313:615–617, 1985
21. Fiala M: A study of the combined role of viruses, mycoplasmas and bacteria in adult pneumonia. Am J Med Sci 257:44–51, 1969
22. Foy HM, Kenny GE, McMahan R, et al: *Mycoplasma pneumoniae* pneumonia in an urban area. JAMA 214:1666–1672, 1970
23. Fraser DW, Tsai TR, Orenstein W, et al: Legionnaires' disease: Description of an epidemic of pneumonia. N Engl J Med 297:1189–1197, 1977
24. Geckler RW, Gremillion DH, McAllister CK, et al: Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. J Clin Microbiol 6:396–399, 1977
25. Grayston JT: *Chlamydia pneumoniae*, strain TWAR. Chest 95:664–669, 1989
26. Grayston JT, Diwan VK, Cooney M, et al: Community- and hospital-acquired pneumonia associated with Chlamydia TWAR infection demonstrated serologically. Arch Intern Med 149:169–173, 1989
27. Grayston JT, Kuo CC, Wang SP, et al: A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. N Engl J Med 315:161–168, 1986
28. Hager H, Verghese A, Alvarez S, et al: *Branhamella catarrhalis* respiratory infections. Rev Infect Dis 9:1140–1149, 1987
29. Heineman HS, Chawla JK, Lofton WM: Misinformation from sputum cultures without microscopic examination. J Clin Microbiol 6:518–527, 1977
30. Hirschmann JV, Everett ED: *Haemophilus influenzae* infections in adults: Report of nine cases and a review of the literature. Medicine (Baltimore) 58:80–94, 1979
31. Holmberg H: Aetiology of community-acquired pneumonia in hospital treated patients. Scand J Infect Dis 19:491–501, 1987
32. Honeybourne D, Andrews JM, Ashby JP, et al: Evaluation of the penetration of ciprofloxacin and amoxycillin into the bronchial mucosa. Thorax 43:715–719, 1988
33. Kerttula Y, Leinonen M, Koskela M, et al: The aetiology of pneumonia: Application of bacterial serology and basic laboratory methods. J Infect 14:21–30, 1987
34. Keys TF: Therapeutic considerations in the treatment of Legionella infections. Semin Respir Infect 4:270–273, 1987
35. Kleemola M, Saikku P, Visakorpi R, et al: Epidemics of pneumonia caused by TWAR, a new *Chlamydia* organism in military trainees in Finland. J Infect Dis 157:230–236, 1988
36. Kobayashi H: Clinical efficacy of ciprofloxacin in the treatment of patients with respiratory tract infections in Japan. Am J Med 82 (suppl 4A):169–173, 1987
37. Kuo CC, Grayston JT: In vitro drug susceptibility of *Chlamydia* sp. strain TWAR. Antimicrob Agents Chemother 32:257–258, 1988
38. Levy M, Dromer F, Brion N, et al: Community-acquired pneumonia: Importance of initial noninvasive bacteriologic and radiographic investigations. Chest 92:43–48, 1988
39. Linz DH, Tolle SW, Elliot DL: *Mycoplasma pneumoniae* pneumonia: Experience at a referral center. West J Med 140:895–900, 1984
40. MacFarlane JT, Finch RG, Ward MJ, et al: Hospital study of adult community-acquired pneumonia. Lancet 2:255–258, 1982
41. Mandell GL, Sande MA: Antimicrobial agents: Penicillins, cephalosporins, and other beta-lactam antibiotics. *In* Gilman AG, Goodman LS, Rall TW, et al (eds): Goodman & Gilman's The Pharmacological Basis of Therapeutics, ed 7. New York, Macmillan, 1985, pp 1115–1149
42. Mandell GL, Sande MA: Antimicrobial agents: Sulfonamides, trimethoprim-sulfamethoxazole, and agents for urinary tract infections. *In* Gilman AG, Goodman LS, Rall TW, et al (eds): Goodman & Gilman's The Pharmacological Basis of Therapeutics, ed 7. New York, Macmillan, 1985, pp 1095–1114
43. Mansel JK, Rosenow EC III, Smith TF, et al: *Mycoplasma pneumoniae* pneumonia. Chest 95:639–646, 1989
44. Marrie TJ: Q fever pneumonia. Semin Respir Infect 4:47–55, 1989
45. Marrie TJ, Grayston JT, Wang SP, et al: Pneumonia associated with the TWAR strain of *Chlamydia*. Ann Intern Med 106:507–511, 1987
46. McKellar PP: Treatment of community-acquired pneumonias. Am J Med 79 (suppl 2A):25–30, 1985
47. McLeod DT, Ahmad F, Power JT, et al: Bronchopulmonary infection due to *Branhamella catarrhalis*. Br Med J 287:1446–1447, 1983
48. Muder RR, Yu VL, Fang GD: Community-acquired Legionnaires' disease. Semin Respir Infect 4:32–39, 1989
49. Murray BE, Moellering RC: Antimicrobial agents in pulmonary infections. Med Clin North Am 64:319–342, 1989
50. Murray PR, Washington JA II: Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin Proc 50:339–344, 1975
51. Musher DM, Kubitschek KR, Crennan J, et al: Pneumonia and acute febrile tracheobronchitis due to *Haemophilus influenzae*. Ann Intern Med 99:444–450, 1983
52. Neu HC: *In vitro* activity of a new broad spectrum, beta-lactamase–stable oral cephalosporin, cefixime. Pediatr Infect Dis 6:958–962, 1987
53. Neu HC: Penicillins. *In* Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases, ed 3. New York, Churchill Livingstone, 1990, pp 230–246
54. Ninane G, Joly J, Kraytman M, et al: Bronchopulmonary infection due to beta-lactamase–producing *Branhamella catarrhalis* treated with amoxycillin/clavulanic-acid. Lancet 1:257, 1978
55. Norris S, Nightingale CH, Mandell GL: Tables of antimicrobial agent pharmacology. *In* Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases, ed 3. New York, Churchill Livingstone, 1990, pp 434–457
56. Pallares R, Gudiol F, Linares J, et al: Risk factors and response to antibiotic therapy in adults with bacteremic pneumonia caused by penicillin-resistant pneumococci. N Engl J Med 317:18–22, 1987
57. Peterson PK, Stein D, Guay DRP, et al: Prospective study of lower respiratory tract infections in an extended-care nursing home program: Potential role of oral ciprofloxacin. Am J Med 85:164–171, 1988
58. Piercy EA, Barbaro D, Luby JP, et al: Ciprofloxacin for methicillin-resistant *Staphylococcus aureus* infections. Antimicrob Agents Chemother 33:128–130, 1989
59. Polk RE: Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med 87 (suppl 5A):76S–81S, 1989
60. Powell OW, Kennedy KP, McIver M, et al: Tetracy-

cline in the treatment of "Q" fever. Aust Ann Med 11:184–188, 1962
61. Rein MF, Gwaltney JM Jr, O'Brien WM, et al: Accuracy of Gram's stain in identifying pneumococci in sputum. JAMA 239:2671–2673, 1978
62. Rudin JE, Evans TL, Wing EJ: Failure of erythromycin in treatment of *Legionella micdadei* pneumonia. Am J Med 76:318–320, 1984
63. Saito A, Koga H, Shigeno H, et al: The antimicrobial activity of ciprofloxacin against *Legionella* species and the treatment of experimental *Legionella* pneumonia in guinea pigs. J Antimicrob Chemother 18:251–260, 1986
64. Sanders CC, Sanders WE Jr, Goering RV: Overview of preclinical studies with ciprofloxacin. Am J Med 82 (suppl 4A):2–11, 1987
65. Schachter J: *Chlamydia psittaci:* "Reemergence" of a forgotten pathogen. N Engl J Med 315:189–191, 1986
66. Smith GH: Oral cephalosporins in perspective. Drug Intell Clin Pharmacol 24:45–51, 1990
67. Standiford HC: Tetracyclines and chloramphenicol. *In* Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases, ed 3. New York, Churchill Livingstone, 1990, pp 284–295
68. Steigbigel NH: Erythromycin, lincomycin and clindamycin. *In* Mandell GL, Douglas RG, Bennet JE (eds): Principles and Practice of Infectious Diseases, ed 3. New York, Churchill Livingstone, 1990, pp 308–317
69. Stratton CW, Hawley HB, Horsman TA, et al: *Hemophilus influenzae* pneumonia in adults: Report of five cases caused by ampicillin-resistant strains. Am Rev Respir Dis 121:595–598, 1980
70. Sullivan RJ Jr, Dowdle WR, Marine WM, et al: Adult pneumonia in a general hospital: Etiology and host risk factors. Arch Intern Med 129:935–942, 1972
71. Tsai TF, Finn DR, Plikaytis BD, et al: Legionnaires' disease: Clinical features of the epidemic in Philadelphia. Ann Intern Med 90:509–517, 1979
72. Van Scoy RE: Bacterial sputum cultures: A clinician's viewpoint. Mayo Clin Proc 52:39–41, 1977
73. Wallace RJ Jr, Musher DM: In honor of Dr. Sarah Branham, a star is born: The realization of *Branhamella catarrhalis* as a respiratory pathogen. Chest 90:447–450, 1986
74. Washington JA, Wilson WR: Erythromycin: Microbial and clinical perspective after 30 years of clinical use I. Mayo Clin Proc 60:189–203, 1985
75. White RJ, Blainey AD, Harrison KJ, et al: Causes of pneumonia presenting to a district general hospital. Thorax 36:566–570, 1981
76. Wollschlager CM, Khan FA, Khan A: Utility of radiography and clinical features in the diagnosis of community-acquired pneumonia. Clin Chest Med 8:393–404, 1987
77. Wollschlager CM, Raoof S, Khan FA: Oral ciprofloxacin in the treatment of 14 patients with bacterial pneumonia. NY State J Med 87:330–333, 1987
78. Woodhead MA, MacFarlane JT, McCracken JS, et al: Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1:671–674, 1987
79. Wright PW, Wallace RJ Jr: Pneumonia due to *Moraxella (Branhamella) catarrhalis.* Semin Respir Infect 4:40–46, 1989
80. Yeaman MR, Mitscher LA, Baca OG: *In vitro* susceptibility of *Coxiella burnettii* to antibiotics, including several quinolones. Antimicrob Agents Chemother 31:1079–1084, 1987

Address reprint requests to

Neil B. Hampson, MD
Section of Pulmonary and Critical Care Medicine
Virginia Mason Clinic
P.O. Box 900
Seattle, WA 98111