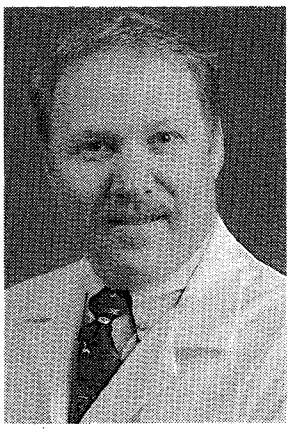
CME ARTICLE

Developing Cost-Effective Guidelines for the Appropriate Use of Antimicrobial Therapy in Respiratory Tract Infection

By Lee R. Weiss, MD, FACEP



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Abstract

This article provides clinicians with a review of the antimicrobial treatment options for pediatric and adult respiratory tract diseases. A discussion of the microbiological epidemiology of common respiratory tract infections and issues relating to their treatment is provided. This information should provide a guideline that will enable clinicians to select the most cost-effective and efficacious therapy to treat a variety of respiratory tract diseases.

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With advances in diagnostic testing and the development of new antimicrobial agents for the treatment of pediatric and adult respiratory tract disease (otitis media, sinusitis, acute exacerbation of chronic bronchitis [AECB], and community-acquired pneumonia [CAP]), the selection of appropriate antimicrobial treatment has become more confusing than ever. An understanding of the microbiological epidemiology of common respiratory tract infections and issues related to resistance will enable clinicians to develop pathways and clinical guidelines that should promote appropriate use of antimicrobials.

Community-acquired pneumonia and AECB continue to contribute significantly to morbidity and mortality in the United States. In 1993 more than 4 million people were diagnosed with pneumonia, nearly one fourth of whom required hospitalization.[1] Specifically, patients aged 65 years and older with CAP accounted for more than 50% of all cases. Clearly, the elderly are at the greatest risk of mortality from pneumonia.

The costs attributable to CAP and AECB are astronomical, with direct costs of $1.5 billion and indirect costs of $5.5 billion in 1990 US dollars.

To develop pathways of appropriate use, primary care clinicians must consider:

- Their choice of appropriate, empiric, first-line therapy
- The emerging patterns of bacterial resistance and how they affect the

selection of antimicrobials in specific patient subsets
- Issues related to patient noncompliance, side-effect profiles, and drug-drug interactions
- Development of tools to determine which patients require hospitalization and which can be discharged and the appropriate switch therapies to prevent rehospitalization.

Etiology: The Microbiological Spectrum of Respiratory Disease

Community-Acquired Pneumonia. CAP is defined as pneumonia that is not acquired in a hospital or nursing home.[2] *Streptococcus pneumoniae* is the single most frequent cause of CAP, accounting for 30% to 70% of the incidence of the disease, depending on geographic location, age, and immunologic status.[3] Over time, agents such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus pyogenes* have seldom occurred, but recently they have been seen with increasing frequency (Table 1).[3]

The availability of more powerful and specific diagnostic tests often has made it possible to identify atypical agents as the cause of CAP. Among those identified, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* sp appear most frequently. In a variety of studies,[4-6] *S. pneumoniae* has been identified as the single most common microbiological pathogen, followed by *M. pneumoniae* and *Legionella* sp.

A review of the literature discloses a striking change in the predominate microbiological epidemiology of CAP, based on age and underlying disease, with patients aged 65 years and younger clearly having *S. pneumoniae*, *M. pneumoniae*, and viral etiologies,[5,6] whereas in patients aged 65 years and older *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella* sp, *H. influenzae*, *Staphylococcus aureus*, mixed flora (aspiration related), and gram-negative bacillary pneumonia predominate. Creation of subsets of patient groups on the basis of age-related microbiological epidemiologic features drives treatment algorithms.

Acute Exacerbation of Chronic Bronchitis. The American Thoracic Society (ATS) defines chronic bronchitis as a condition characterized by cough and the production of sputum for 3 consecutive months in 2 consecutive years.[6] Not all patients fit this definition, and there

Table 1. Microbiological Pathogens in Community-Acquired Pneumonia

Microbiologic Cause	Prevalence (%) N. American Studies	Prevalence (%) British Thoracic Society
Bacterial	20-60	60-75
Streptococcus pneumoniae		
Haemophilus influenzae	3-10	4-5
Staphylococcus aureus	3-5	1-5
Gram-negative bacilli	3-10	Rare
Miscellaneous	3-5	—
Atypical Agents	10-20	—
Legionella	2-8	2-5
Mycoplasma pneumoniae	1-6	5-18
Chlamydia pneumoniae	4-6	—
Viruses	2-15	8-16
Aspiration	6-10	—

Source: Bartlett JG. IDCP guidelines: Lower respiratory tract infections. *Infect Dis Clin Pract* 1996;5:147-167. See reference 3.

Table 2. Causes of Acute Exacerbation of Chronic Bronchitis

Viral	Influenza virus
	Rhinovirus
	Parainfluenza virus
	Coronavirus
Common Bacteria	*S. pneumoniae*
	H. influenzae (nontypable)
	M. catarrhalis
Uncommon Bacteria	*M. pneumoniae*
	C. pneumoniae
	B. pertussis
	P. aeruginosa
Noninfectious—Environmental Factors	Allergies
	Asthma
	Air pollutants
	Toxic industrial gases
	Cigarette smoke

Source: Chodosh S. Treatment of acute exacerbations of chronic bronchitis: State of the art. *Am J Med* 1991;91(suppl 6A):87S-92S.

is widespread disagreement among clinicians over whom to treat for AECB, with many clinicians classifying their patients in various ways.

In 1987, Anthonisen and associates[7] reported on a double-blind, placebo-controlled trial in which they looked at placebo versus antimicrobial therapy in the treatment of AECB. They concluded that antimicrobial treatment was beneficial for so-called "type I" exacerbation patients, who had increased dyspnea, sputum volume, and sputum purulence. When all three signs and symptoms that usually comprise AECB were present, antimicrobial therapy had a better end result than placebo.[7]

Acute exacerbation of chronic bronchitis has been attributed to infectious and noninfectious causes (Table 2). Viral infections account for 20% to 30% of AECB.[8-12] Viral etiologies include influenza, rhinovirus, parainfluenza, and coronavirus.[10-12] Bacterial exacerbation is believed to account for 10% to 50% of AECB.[8] The bacteria most often isolated include *S. pneumoniae*; *H. influenzae*, which cannot be typed; and *M. catarrhalis*.[13,14] Less common bacterial etiologies include *M. pneumoniae*, *C. pneumoniae*, *Bordetella pertussis*,[3,15] and *Pseudomonas aeruginosa*.

Table 3. Prevalence of β-Lactamase–Mediated Ampicillin Resistance Among Clinical Isolates of *H. influenzae* in North America: 1983-1995

Country	Years	No. of Isolates	No. of Centers	% Resistant
USA	1983-1984	3356	22	15%
Canada	1985-1988	2503	14	17%
USA	1986	2811	30	20%
USA	1987-1988	564	15	17%
Canada	1991	702	8	25%
Canada	1992-1993	1688	23	28%
USA	1992-1993	800	19	30%
USA	1993	5750	28	32%

Source: Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med* 1995;99(suppl 6B):3S-7S

Noninfectious environmental factors can also trigger exacerbations of chronic bronchitis.[16,17] Such factors include air pollutants, toxic industrial agents, carbon monoxide, and cigarette smoke. Concomitant conditions, including asthma, malignancies, coronary artery disease, and obesity, can contribute to an acute exacerbation.[17]

Emerging Patterns of Bacterial Resistance

Without question, the development of resistance in *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* represents one of the greatest challenges to the management of infectious respiratory disease that faces clinicians today.

From 1983 to 1993, β-lactamase–mediated resistance to ampicillin rose steadily among *H. influenzae* isolates (Table 3).[18,19] The percentage of β-lactamase–producing strains of *H. influenzae* doubled from 15% in 1983 to 32% in 1993.[18,19] Concomitant resistance of β-lactamase–producing strains of *H. influenzae* to other penicillins and cephalosporins has not only been demonstrated but arguably drove the pharmaceutical industry of the 1980s to develop advanced-generation cephalosporins as well as other agents.[19-21]

In a 1992 survey of 19 US medical centers, 30% of *H. influenzae* isolates were β-lactamase positive. Of the agents tested, cefaclor, loracarbef, and cefprozil appeared to be less active, whereas amoxicillin-clavulanate, cefuroxime axetil, cefixime, and ciprofloxacin retained good activity.

A retrospective examination of the occurrence of β-lactamase–producing *H. influenzae* and the impact of this particular microorganism on the treatment of respiratory tract disease in adults and children led to the critical conclusion that the solution to this seemingly problematic microorganism was not the development of advanced-generation cephalosporins, β-lactamase inhibitor-associated penicillins, or fluoroquinolones but rather was related to the widespread use of an extremely effica-

cious *H. influenza* B vaccine over the past decade.[22-24]

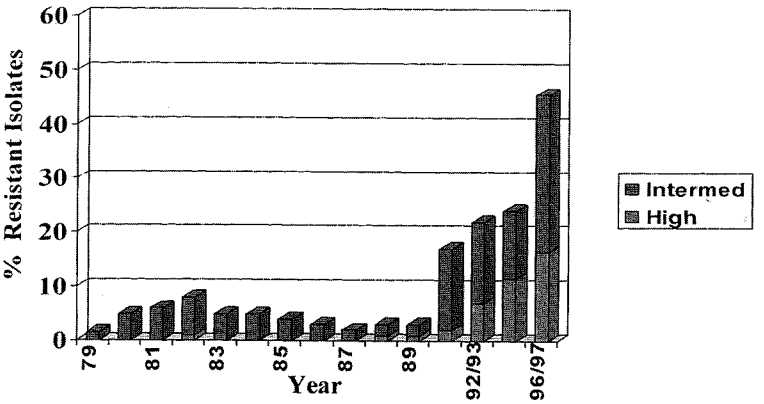
Streptococcal pneumoniae is a primary pathogen associated with lower respiratory tract infections. It is rapidly and increasingly becoming resistant to penicillin and other antibiotics. The relative susceptibility of *S. pneumoniae* is classified as being susceptible, intermediate, or high-level resistant.

Susceptibility is defined as having a *S. pneumoniae* isolate with a minimum inhibitory concentration 90 (MIC_{90}) against penicillin of less than 0.06 µg/mL. Intermediate resistance is defined as having a *S. pneumoniae* isolate with a MIC_{90} against penicillin of between 0.1 and 1.0 µg/mL. High-level resistance is defined as having a *S. pneumoniae* isolate with a MIC_{90} against penicillin of greater than 2.0 µg/mL. During the 1980s, *S. pneumoniae* demonstrated a low level of penicillin resistance (3% to 7%). By contrast, in 1991 its overall resistance was measured at 17.2%.[20] Increasing resistance has been demonstrated (Figure 1).[20]

In 1992-1993, penicillin resistance was seen in 22% of *S. pneumoniae* strains (with 15% intermediate resistance and 7% high resistance).[25] By 1994-1995, 23.6% of *S. pneumoniae* strains were found to have some degree of penicillin resistance (14.1% with intermediate resistance and 9.5% with high resistance).[25]

The clinical relevance of penicillin resistance has still to be established. At present, failures to penicillin therapy have been reported in patients with demonstrated penicillin-resistant *S. pneumoniae*-related meningitis. *S. pneumoniae* is also demonstrating resistance to other antibiotics, including cefotaxime (3%), ceftriaxone (5%), cefuroxime (12%), chloramphenicol (4%), trimethoprim-sulfamethoxazole (18%), and the macrolides azithromycin, clarithromycin, and erythromycin (10% combined).[25]

Figure 1. Penicillin Resistance to *S. pneumoniae* in the United States



Sources: Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med* 1995;99(suppl 6B):3S-7S. Jones RN, et al. SENTRY study, 1997. See reference 18.

Table 4. In Vitro Activity of Selected Cephalosporins by MIC_{90}

Organism	Cephalexin	Cefaclor	Loracarbef	Ceftibuten	Cefixime	Cefuroxime
S. pnuemoniae	2	0.5	0.5	8	4	<0.06
S. pyogenes	2	0.5	0.5	2	0.5	<0.06
S. aureus	4	4	4	>32	>32	4
H. influenzae	8	8	4	0.06–2	0.5	0.5
M. catarrhalis	4	1	2	0.25–4	0.6	0.5

Source: Kucers A, Bennett Mck N. *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis*. 5th ed. Philadelphia: JB Lippincott; 1997.

Resistance rates to oral advanced-generation cephalosporins are often a significant surprise to primary care clinicians. Dagan and associates found marked resistance to cefaclor and to a lesser extent cefuroxime in children with drug-resistant *S. pneumoniae*-related acute otitis media.[26]

It is becoming increasingly clear that orally administered advanced-generation cephalosporins, including agents considered to be gold standards for the treatment of *S. pneumoniae*, are not the oral equivalent of the parenterally administered third-generation cephalosporin counterparts such as ceftriaxone and cefotaxime (Table 4).[26-28]

The recent increase in the use of advanced-generation macrolides (azithromycin and clarithromycin) has drawn attention to an increase in macrolide resistance in *S. pneumoniae*. Resistance rates of *S. pneumoniae* vary by geographic region and antimicrobial class, as well as by the method used to measure resistance (Table 5). A study conducted in Atlanta, Georgia, found *S. pneumoniae* resistance rates of 9% for cefotaxime, 15% for erythromycin, 26% for trimethoprim-sulfamethoxazole, and 25% for multiple agents in 431 hospitalized patients.[29]

The methodology used in performing susceptibility testing can have an overwhelming impact on predicting sensitivity, resistance patterns, and drive utilization. Determining the MIC_{90} levels by the micro-broth dilution technique or by "E testing" can be very procedure sensitive and intensive. Clinicians who are neither microbiologists nor infectious disease-trained specialists may be unaware of the complexity of performing these techniques. Conducting micro-broth dilution or E testing in various oxygen-rich or poor environments can overestimate macrolide resistance two- to threefold.[30]

Considerable controversy also surrounds assigning breakpoint standards recommended by the National Committee on Clinical Laboratory Standards and how these standards actually affect the use of different antimicrobials in clinical practice.

Susceptibility testing of macrolide resistance requires a significant degree of laboratory and technical sophistication, as well as strict adherence to a reproducible technique that is not available in most laboratories and certainly not to most clinicians. A careful review of testing performed under strict technical controls with a high degree of reproducibility discloses that macrolide resistance in *S. pneumoniae* is between 10% and 12%.[18,31-39] The exact clinical impact of this finding has still to be demonstrated, because the vast majority of clinicians have not seen and probably will not see demonstrated treatment failures as a result of proven macrolide resistance in respiratory tract-related infections secondary to *S. pneumoniae*.[33]

An examination of macrolides as a class also reveals that resistance to them in *S. pneumoniae* is class specific. However, it is becoming increasingly clear that some macrolides are more likely than others to lead to class-specific resistance in *S. pneumoniae*.

The Finnish Study Group for Antimicrobial Resistance demonstrated the results of limiting the type and use of macrolides on the occurrence of resistance in group A streptococci in Finland.[40] A closer examination of this

Table 5. In Vitro Susceptibilities of Erythromycin, Azithromycin, and Clarithromycin

Organism	Erythromycin MIC_{90}	Azithromycin MIC_{90}	Clarithromycin MIC_{90}
S pneumoniae	0.015–1	0.12–2	0.015–0.06
S pyogenes	0.03–4	0.12–4	0.012–2
M. catarrhalis	0.25–2	0.03–0.5	0.06–0.12
H influenzae	2–32	0.25–4	0.4–2
M pneumoniae	0.004–0.02	0.01–0.12	0.004–0.05

Source: Kucers A, Bennett Mck N. *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis.* 5th ed. Philadelphia: JB Lippincott; 1997.

study reveals a study population and antibiotic dynamics that are similar to those in the United States. Overuse of specific macrolide antibiotics clearly drives streptococcal resistance.

Leach and colleagues studied the effects of single-dose azithromycin, which was used to treat childhood trachoma in aboriginal children in Australia, on the carriage and resistance of *S. pneumoniae*. The proportion of carriage-positive azithromycin-resistant *S. pneumoniae* strains was 1.9% per single-dose azithromycin therapy, rising to a maximum of 54.5% and persisting for as long as 6 months after a single dose of azithromycin.[41] High rates of nasopharyngeal carriage of azithromycin-resistant *S. pneumoniae* can have a potentially devastating effect on the efficacy of this important class of antimicrobials.

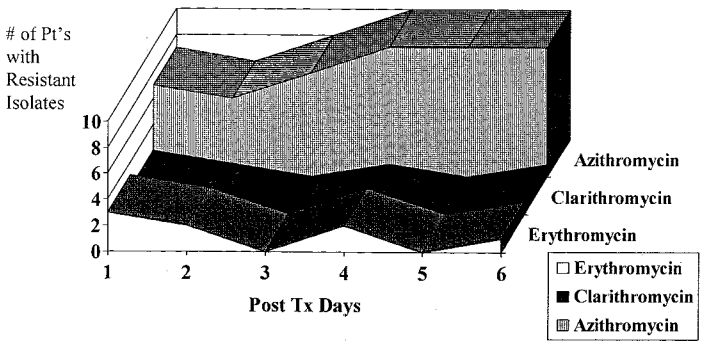
Guggenbichler and colleagues have reported on the effects of macrolides on respiratory flora (Figure 2).[42] Children treated with macrolide antibiotics for respiratory tract infections were followed linearly for the development of macrolide-resistant *S. pneumoniae* isolated by the nasopharyngeal swab technique. When comparing children who were treated with erythromycin, clarithromycin, and azithromycin, those who were treated with azithromycin were 10-fold more likely to develop macrolide-resistant *S. pneumoniae* nasopharyngeal colonization.

Over the past 3 years, there has been an exponential increase in the use of azithromycin for the treatment of mild to moderate respiratory tract infections in the United States. The implications for the development of nasopharyngeal colonization with macrolide-resistant *S. pneumoniae*, which has been demonstrated to persist for months in ambulatory, otherwise healthy patients, represents a significant threat to the entire macrolide class. The overuse of azithromycin is likely to be driving macrolide resistance in *S. pneumoniae* on a class basis.

Antimicrobial coverage of *S. pneumoniae* in CAP and AECB with second-generation fluoroquinolones (ciprofloxacin and ofloxacin) is problematic and marginal at best. With the introduction of fluoroquinolenes into the antimicrobial marketplace, second-generation fluoroquinolone-related *S. pneumoniae* resistance developed more quickly than anticipated, largely on the basis of an amino acid substitution (phenylalanine or tryptophan) at the serine$_{80}$ position of the topoisomerase IVA subunit of the DNA gyrase (GrlA). Point mutation-related resistance in the newer fourth-generation fluoroquinolones, including sparfloxacin, grepafloxacin, and trovafloxacin, occurs in the same manner as in the second-generation fluoroquinolones, albeit at a low frequency and in a two-step process. The antibacterial activity of grepafloxacin is generally similar to that of sparfloxacin and levofloxacin.[43-47]

Grepafloxacin is more active in vitro against pneumococci than ciprofloxacin, including strains of pneumococci that are highly resistant to penicillin.[43-47] Grepafloxacin, levofloxacin, sparfloxacin, and trovofloxacin are also highly active against other respiratory patho-

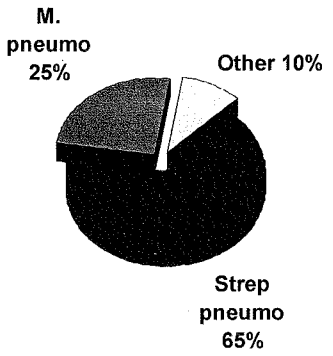
Figure 2. Influence of Macrolides on Oral Flora



Source: Guggenbichler JP. Influence of Macrolides on Oral Flora. Presented at the First World Congress of Pediatric Infectious Diseases, December 1996, Acapulco, Mexico.

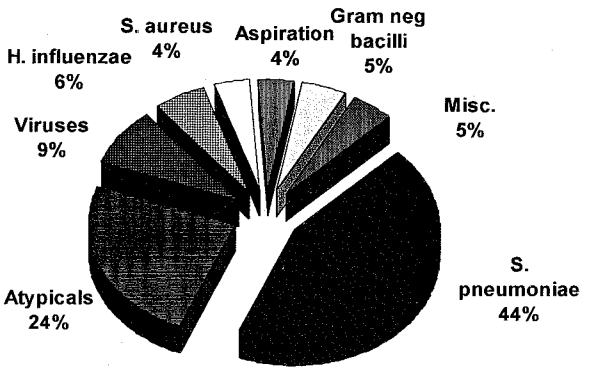
gens, including *H. influenzae*, *M. catarrhalis*, *Legionella pneumophilia*, *C. pneumoniae*, and *M. pneumoniae*. In the case of grepafloxacin, and especially trovofloxacin, additional anaerobic coverage is noted.[45,47-54]

Figure 3. Emerging Patterns of Bacterial Resistance: The Microbiological Spectrum of Respiratory Disease: Community-Acquired Pneumonia Among Patients Younger than Age 65 Years with No Comorbid Disease



Source: Bartlett JG. IDCP guidelines: Lower respiratory tract infections. *Infect Dis Clin Pract* 1996;5:147-167

Figure 4. Emerging Patterns of Bacterial Resistance: The Microbiological Spectrum of Respiratory Disease: Community-Acquired Pneumonia Among Patients Older than Age 65 Years With or Without Comorbid Disease



Source: Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995;333:1618-1624.

In numerous clinical trials, grepafloxacin, sparfloxacin, levofloxacin, and trovofloxacin were as effective but not superior to cefuroxime axetil 250 mg twice a day, ofloxacin 200 mg twice a day, amoxicillin 500 mg three times a day, ciprofloxacin 500 mg twice a day, amoxicillin/clavulanate 500/125 mg three times a day, or erythromycin 1 g twice a day.[53,55-59] Grepafloxacin, sparfloxacin, and levofloxacin appear to be effective for once-daily treatment of CAP and AECB. Whether their superior in vitro activity against penicillin-resistant pneumococci offers any clinical advantage over older fluoroquinolones or advanced-generation macrolides remains to be determined.[60]

Trovofloxacin has the best in vitro activity against common respiratory pathogens of any of the available fourth-generation fluoroquinolones, including anaerobes, but to date almost no clinical studies have been published. Trovofloxacin offers the possibility of single-agent coverage of a wide range of infections.

There continues to be concern about superinfection and overuse in inappropriate patient subsets, as well as the significant threat of the emergence of fluoroquinolone-resistant microorganisms. Like their second-generation fluoroquinolone counterparts, discretion and limiting the use of trovofloxacin, as well as all fourth-generation fluoroquinolones, to the treatment of mixed infections in which anaerobes may be involved is advised.[54]

Treatment of CAP and AECB

Empiric Therapy. Empiric treatment guidelines were formulated for patients with CAP, based on patient age, disease severity, microbiological epidemiology, patient subsetting, and the absence/presence of comorbid conditions by the ATS in 1993 and by the Infectious Disease Society of America (ISDA) in 1998 (Figures 3-5).[61,62]

For patients younger than age 60 years who have no comorbid conditions

and do not require hospitalization, both the ATS and the IDSA guidelines advocate the use of a macrolide (especially azithromycin or clarithromycin, where *H. influenzae* or *S. pneumoniae* is suspected) or tetracycline in those who cannot tolerate macrolides.[61-63]

The more recent IDSA guidelines advocate the use of an advanced-generation fluoroquinolone (sparfloxacin, grepafloxacin, or trovafloxacin) instead of tetracycline for patients who are intolerant of macrolide therapy. Considering the advanced-generation fluoroquinolones, patients who take sparfloxacin have demonstrated considerable problems with photodermatitis (8% to 10%) that persisted for 1 or more weeks after therapy and occurred as a result of exposure to indirect sunlight, as well as a shortening of the QT interval that resulted in numerous reports of torsades de pointes, limiting the drug's overall usefulness.[60,64-66]

Patients who take grepafloxacin have been reported to have significant problems with taste perversion and nausea, necessitating treatment withdrawal (as many as 25% at a 600-mg/day dosage). Grepafloxacin treatment (especially at the 600-mg/day dosage) has been associated with diarrhea, dizziness, headache, tendonitis, and spontaneous tendon rupture, all of which have significantly limited grepafloxacin's widespread clinical use.[49,51,53,60,61]

Levofloxacin, the pure L-enantiomer of ofloxacin, bears special scrutiny. At the recommended dosage of 500 mg/day, levofloxacin has little more L-ofloxacin than the ofloxacin racemic mixture at 400 mg twice a day. Whether this product is actually an advanced-generation fluoroquinolone and offers any real advantage over ofloxacin remains to be demonstrated by widespread, randomized, blinded clinical trials.[56]

With trovofloxacin, at 200 mg/day, the most common side effects are euphoria, dizziness, and memory loss.[64] Resistance to fluoroquinolones, like their macrolide counterparts, is probably class specific. Cautious use of the advanced-generation fluoroquinolones is emphasized, because of the problems of bacterial overgrowth and resistance that developed so quickly in the second-

Figure 5. 1993 ATS Recommendations for Treatment of Patient Subsets with CAP

Patient Subset	Antibiotic Recommendation	Comments
Outpatient <60 years of age without significant comorbidity	Macrolide Erythromycin Clarithromycin or Azithromycin or Tetracycline	Advanced-generation macrolides, especially for patients at risk of *H. influenzae* (smokers) or those who are intolerant of erythromycin. Use tetracyclines for those who are intolerant or allergic to macrolides
Outpatients >60 years of age without comorbid disease	Second-generation cephalosporins or TMP-SMX or beta-lactam/beta-lactamase inhibitor with or without macrolide therapy	Macrolide therapy indicated for suspected legionellosis
Hospitalized patients with CAP	Second- or third-generation cephalosporin or beta-lactam/beta-lactamase inhibitor with or without macrolide therapy	Macrolide therapy for patients with suspected legionellosis; rifampin may be added for documented legionellosis
Patients with severe CAP (excluding suspected/documented HIV-related pneumonia)	Macrolide plus third-generation cephalosporin with pseudomonal activity or other anti-pseudomonal agent like imipenem/cilastin or ciprofloxacin with an aminoglycoside	Add aminoglycoside for the first several days of therapy

Source: 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

generation products, ciprofloxacin and ofloxacin.[66-69] The continued use of ciprofloxacin and ofloxacin in low-dose short course regimens for lower urinary tract infections is a matter of concern. Rapid development of *Streptococcus viridans* and *Streptococcus epidermicus* resistance during and after treatment has been observed in patients who are treated with these regimens.

The original ATS guidelines for patients older than age 60 years who have no comorbidity or only modest comorbidity but who could be treated as outpatients called for this patient population be treated with a second-generation cephalosporin (cefuroxime axetil or amoxicillin/clavulanate) with the addition of a macrolide if legionella was suspected.[61,62,70-72]

The frequency of atypical microorganisms as the cause of pneumonia in this patient subset (>20%) suggests that advanced-generation macrolides (azithromycin/clarithromycin) can be considered as first-line agents for these patients, with advanced-generation fluoroquinolones (sparfloxacin, grepafloxacin, and trovofloxacin) serving as alternatives for patients with more extensive comorbid disease, who may appear clinically sicker or who are intolerant of macrolide therapy (Figures 6 and 7).[73-77]

For patients with pneumonia who have nonproductive coughs, empiric therapy is usually initiated. The promise of the polymerase chain reaction (PCR) technique to identify the specific microorganism and potentially the antibiotogram of the microorganism based on gene amplification technology has yet to be realized and is not widely available. There is good reason to be enthusiastic about the promise of PCR technology and the clinical impact it will have on pathogen identification and antimicrobial product selection.

At present, patients with productive coughs from whom sputum is available can be treated with pathogen-directed therapy. Patients in whom *S. pneumoniae* has been identified as the cause of CAP should be treated with microorganism-specific therapy.[56,78] However, the clinician must establish whether the patient is at risk for multidrug-resistant *S. pneumoniae* and if so institute appropriate therapy.

Patients at the greatest risk include children younger than age 36 months,

Figure 6. Current Recommendations for the Empiric Therapy of Outpatient Community-Acquired Pneumonia

Macrolide Therapy
Clarithromycin, Azithromycin, or Erythromycin
or
Fluoroquinolone Therapy
Grepafloxacin, Sparfloxacin, or Trovafloxacin
or
Doxycycline
or
For patients older than 60 years of age and/or with significant comorbid disease
Amoxicillin-clavulanate
or
Second-generation cephalosporin
(cefuroxime axetil, cefprozil, cefpodoxime)

Source: Consensus statement: Therapeutic recommendations for community-acquired pneumonia and acute exacerbations of chronic bronchitis. *Hosp Med* 1997; 33(suppl):26-27.

Figure 7. Current Recommendations for Hospitalized Immunocompetent Adults with Community-Acquired Pneumonia

Second- or third-generation cephalosporin*
(parenteral ceftriaxone or cefotaxime)
plus
Macrolide†
(azithromycin or clarithromycin)
or
Fluoroquinolone‡
(grepafloxacin, levofloxacin, or trovafloxacin)

*Consider the addition of vancomycin if DRSP is suspected.
†Avoid parenteral erythromycin because of poor tolerability. Rifampin may be added for documented legionellosis.
‡Consider the addition of clindamycin for suspected aspiration pneumonia for patients treated with grepafloxacin or levofloxacin but not trovafloxacin.
Source: Consensus statement: Therapeutic recommendations for community-acquired pneumonia and acute exacerbations of chronic bronchitis. *Hosp Med* 1997; 33(suppl):26-27.

Figure 8. Antimicrobial Agents for CAP Caused by Microbial Pathogens

Pathogen	Drug of Choice	Alternative Drugs	Comments
S. pneumoniae	Penicillin	Cephalosporins Macrolides Vancomycin	DRSP increasing – use third-generation cephalosporins, vancomycin. Avoid azithromycin in instances of suspected bacteremia.
H. influenzae	Second-/third-generation cephalosporin TMP/SMX	Fluoroquinolone Doxycycline	β-lactamase production >30% of strains
S. aureus	Nafcillin/oxacillin ± aminoglycoside	Cephalosporins Vancomycin (MRSA)	MRSA rare in CAP
M. catarrhalis	Second- or third-generation cephalosporin	Advanced-generation macrolide Fluoroquinolone	β-lactamase-producing strains and ampicillin resistance >90% of strains
C. pneumoniae	Doxycycline Erythromycin	Clarithromycin Fluoroquinolones	
Legionella sp	Erythromycin Ciprofloxacin	Clarithromycin Levofloxacin Trovafloxacin	Erythromycin is the most studied, rifampin is frequently added.
M. pneumoniae	Doxycycline Erythromycin	Clarithromycin Fluoroquinolones	
Anaerobes—mixed flora	Clindamycin	High-dose PCN Metronidazole Carbapenem Trovafloxacin	High-dose PCN and clindamycin are the most studied
Gram-negative bacilli	Second- or third-generation cephalosporin	Fluoroquinolone	Uncommon cause of CAP <3%

Source: King DE, Pippin HJ. Community-acquired pneumonia in adults: Initial antibiotic therapy. *Am Fam Physician* 1997;56:544-550.

patients who are immunocompromised, patients who are chronically taking antibiotics, institutionalized patients, or patients who have recently been hospitalized. Currently, such patients should be empirically treated with a third-generation cephalosporin (cefotaxime or ceftriaxone), clindamycin, or vancomycin (Figure 8). Because of the significant threat of vancomycin resistance, this product should be reserved for patients who are the most clinically ill or for those with demonstrated multidrug-resistant *S. pneumoniae.*

Although advanced-generation fluoroquinolones (sparfloxacin, grepafloxacin, and trovafloxacin) have demonstrated superior in vitro activity against penicillin-resistant *S. pneumoniae*, whether these products offer any clinical advantage over older fluoroquinolones or other types of drugs for the management of patients with pneumonia secondary to drug-resistant *S. pneumoniae* (DRSP) remains to be determined (Figures 9 and 10).

Until further studies are completed, patients with DRSP-related pneumonia would best be treated with third-generation cephalosporins (cefotaxime or ceftriaxone), clindamycin, or vancomycin. Patients at intermediate or low risk can be treated with penicillin or ampicillin. Alternatives include first- or second-generation cephalosporins, macrolides (azithromycin, clarithromy-

cin, or erythromycin), or advanced-generation fluoroquinolones (sparfloxacin, grepafloxacin, or trovafloxacin).

Preferred agents for treating patients with CAP secondary to *H. influenzae* or *M. catarrhalis* include a second- or third-generation cephalosporin (cefuroxime, cefotaxime, or ceftriaxone), trimethoprim-sulfamethoxazole, doxycycline, advanced-generation macrolides (azithromycin or clarithromycin), a ß-lactam/ß-lactamase inhibitor (ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam, amoxicillin/clavulanate), or a fluoroquinolone. For *S. aureus*, patients should be treated with nafcillin/oxacillin, with or without rifampin, or gentamicin if the isolate is methicillin-sensitive. Alternative methicillin-sensitive *S. aureus* treatment regimens include cefazolin, cefuroxime, and trimethoprim-sulfamethoxazole. Methicillin-resistant *S. aureus* infections should be treated with vancomycin with/without rifampin/gentamicin, until full antibiotogram information is available (Figure 8).

For the atypical pathogen *Legionella* sp, the preferred agents are macrolides (clarithromycin or azithromycin) or fluoroquinolones (ciprofloxacin, grepafloxacin, levofloxacin, ofloxacin, sparfloxacin, or trovafloxacin), with or without rifampin. For the treatment of *M. pneumoniae* and *C. pneumoniae*, doxycycline or macrolide therapy is preferred; a second-generation fluoroquinolone

Figure 9. Comparative In Vitro Activity of Selected Fluoroquinolones by MIC_{90}

Microorganism	Levofloxacin	Sparfloxacin	Ciprofloxacin
Streptococcus pneumoniae	1	0.5	2
Staphylococcus aureus	0.5	0.1	1
Haemophilus influenzae	0.25	0.06	0.06
Klebsiella pneumoniae	0.25	0.25	0.12
Legionella pneumophilia	0.125	0.06	0.06
Mycoplasma pneumoniae	0.5	0.125	2
Chlamydia pneumoniae	0.5	NA	NA

Source: Formulary 1997;32:926-943

Figure 10. New Fluoroquinolones in Acute Exacerbation of Chronic Bronchitis: US Multicenter Clinical Experience

Drugs and Dosage	Duration (Mean Days)	Clinical Response (No.)	Bacteriological Response	Overall Drug-Related Adverse Events	Most Common Drug-Related Adverse Events
Levofloxacin PO 500 mg qd (187)	6.6	92% (154)	94% (103)	7% (187)	Nausea 2.1%
Cefaclor PO 250 mg tid (186)	8.7	92% (155)	87% (89)	4.9%	Diarrhea 2.2%
Levofloxacin PO 500 mg qd (248)	7	95% (222)	96% (134)	9.9%	Vaginitis 4%
Cefuroxime axetil PO 250 mg bid (244)	10	93% (229)	93% (147)	7.9%	Diarrhea 3%
Sparfloxacin PO 400 mg loading dose then 200 mg qd (395)	10	85.4% (in bacteriologically evaluable patients)		35.2%	Photosensitivity 8.1%
Ofloxacin PO 400 mg bid (403)	10	88.8% (in bacteriologically evaluable patients)		40.4%	Insomnia 14.9%

Source: File TM Jr. New therapeutic options for community-acquired pneumonia and acute exacerbations of chronic bronchitis. *Hosp Med* 1997;33(suppl):18-23.

(ciprofloxacin or ofloxacin) may be substituted. Additional information on the activity of the advanced-generation fluoroquinolones against *C. pneumoniae*- and *M. pneumoniae*-related CAP is required before these products should be routinely recommended.[56,73,76,79,80]

Acute Exacerbation of Chronic Bronchitis. The continued debate regarding the benefit of antibiotics in the treatment of AECB seems for now to be on the side of treating with antibiotics. Initially, reports dating from the 1970s failed to prove a significant short- or long-term benefit from the routine use of antibiotics; however, the results of subsequent studies have been conflicting.[1,7-14] A study of patients with AECB and chronic obstructive pulmonary disease (COPD) that looked at the results of antibiotics versus placebo found symptom resolution in 68% of the antibiotic-treated patients as opposed to 55% of patients treated with placebo.[7]

In a meta-analysis of nine studies involving several hundred patients, there was a slight advantage for the patients treated with antibiotics.[28] Some patients clearly demonstrated a benefit from antibiotic treatment, but it was difficult to differentiate them from the entire population of patients with AECB.

At present, it is recommended that patients with AECB be treated with antibiotics. A variety of agents are currently recommended for the routine treatment of AECB (Figure 11). In general, the microbiologic epidemiology of disease includes *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*; viruses (influenza virus, rhinovirus, parainfluenza virus, and coronavirus); and less commonly *C. pneumoniae*, *M. pneumoniae*, *B. pertussis*, and *Pseudomonas aeruginosa*.

Initial antimicrobial therapy includes ampicillin; doxycycline; ß-lactam/-lactamase inhibitors (amoxicillin/clavulanate, ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam); second- and third-generation cephalosporins (cefuroxime axetil, cefpodoxime, cefprozil, cefotaxime, or ceftriaxone); advanced-generation macrolides (azithromycin or clarithromycin); second- and fourth-generation fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, grepafloxacin, or trovafloxacin); or trimethoprim-sulfamethoxazole.[22]

Use of the PCR technique on patients with AECB has drawn increased attention to the frequency of atypicals as the cause of AECB. For coverage of *C. pneumoniae*, *Legionella* sp, or *C. pneumoniae*, one of the advanced-generation macrolides (clarithromycin) or fluoroquinolones (ofloxacin, levofloxacin, grepafloxacin, sparfloxacin, or trovafloxacin) should be considered, because these drugs offer expanded coverage of both typical and atypical pathogens.

Respiratory Infection Management System (RIMS). Development of standards of care for the management of respiratory tract infections is desirable for many reasons, among them the overall prevalence of such infections and the total cost of care. Overuse of antibiotics has not led to improved care; to the contrary, it has resulted in an increased incidence of resistance, especially in *S. pneumoniae*. Emerging standards of care seem to focus on appropriate antibiotic selection, patient characteristics, and the role of adjunctive therapy. At present, there is little concrete information on current provider (primary care physician or spe-

Figure 11. Antibiotic Choices for the Treatment of Acute Exacerbation of Chronic Bronchitis

- Amoxicillin
- Amoxicillin/clavulanate
- Azithromycin, clarithromycin
- Trimethoprim-sulfamethoxazole
- Doxycycline
- Second- or third-generation cephalosporins (cefprozil, cefpodoxime, cefuroxime axetil)
- Fluoroquinolone (ofloxacin, ciprofloxacin, levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin)

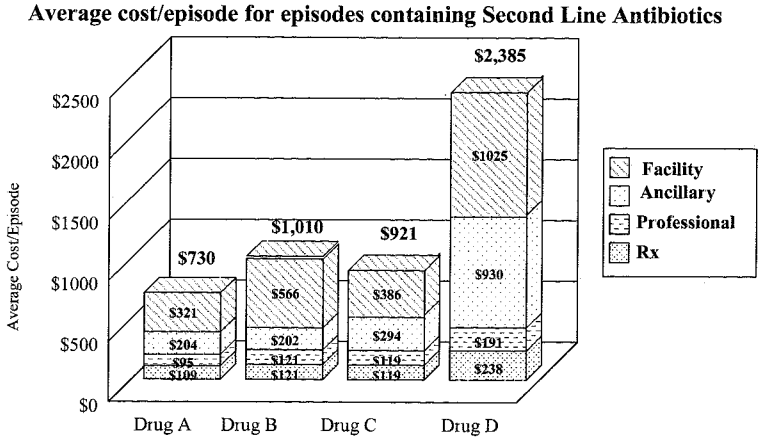
Source: Gotfried MH. Diagnosis and management of acute exacerbations of chronic bronchitis. *Hosp Med* 1997;33(suppl):2-4

cialist) practice patterns, leaving both patients and physicians confused about who really benefits from care.

The National Disease Therapeutic Index shows that respiratory tract infections are the single most common reason for visiting a physician in the United States.[81] Gonzales and colleagues clearly demonstrated that the use of antibiotics in respiratory tract infections was pervasive and potentially inappropriate.[82] Inappropriate antibiotic use was closely linked to female gender and rural location and was not associated with age, geographic location, physician specialty, or payer source.[82]

The Respiratory Management System was developed to determine antibiotic usage patterns in bronchitis and sinusitis to quantify the difference in the total cost of care and use based on the choice (or lack of choice) of antibiotics and to determine whether the increased cost of total care based on antibiotic choice correlated with comorbidity or severity of illness.[83]

Figure 12. Major Cost Components of Bronchitis



Source: Ober NS. Respiratory infection management system. ICMASK IV. 1998;278: 901-904.

The RIMS 1 investigation looked at a 280,000-member independent practice association (IPA) model health plan for a 1-year period. Patients aged 18 years or older who were continuously enrolled in the IPA for a 1-year period and were seen for one or more office visits for bronchitis or sinusitis were analyzed with respect to treatment (no antibiotic or first- or second-line antibiotic therapy).

Each patient was assigned a comorbidity score and a severity score. Diagnostic groupings were made, using the American Health Care Peer Review Clinical Classifications for Health Policy and Research system. Outcome measures included length of episode, cost of care, and number of services.

Sinusitis and bronchitis were extremely prevalent in the RIMS 1 study. In a 1-year period in the 280,000-patient study population, 26,617 patients (33,218 treatment episodes) with AECB and 19,006 patients (22,688 treatment episodes) with sinusitis were seen. Antibiotic use was also prevalent, with 78% of sinusitis patients and 64% of AECB patients receiving antibiotics.

The cost of care of respiratory tract infections (RTIs) was expensive and could be broken down into three factors: 85% of the total cost of RTI was for medical care (nonprofessional services, ie, emergency department costs, imaging center costs, surgicenter costs, hospital costs; ancillary services; laboratory costs; the cost of X rays, injections, vaccinations, and procedures; and the cost of professional services). Eight percent of the total outlay for care went to treatment costs related to the cost of antibiotic therapy, and 7% went for the cost of nonantibiotic therapy.

The total per member per month (PMPM) cost to treat sinusitis was $3.06. Patients with more than one treatment episode represented 52% of the $10,294,000 total cost to treat sinusitis in a 280,000-member IPA over the course of 1 year. The total PMPM cost to treat bronchitis was $5.44. Patients with more than one treatment episode represented

53% of the $18,312,000 total cost to treat AECB in a 280,000-member IPA over the course of 1 year.

The average cost of care for second-line antibiotics to treat a single course of bronchitis varied widely (Figure 12). The statistical significance of comorbidity and severity scores did not vary. Specific antibiotics (azithromycin and cefuroxime) were consistently associated with a higher cost of care per episode of sinusitis and bronchitis (a finding that was reproducible in other RIMS studies at different geographic locations and in different types of practice models).

Of the second-line antibiotics evaluated to treat sinusitis and AECB, amoxicillin/clavulante, azithromycin, clarithromycin, and cefuroxime axetil had very similar endpoints (clinical response rates), whereas the costs were very different.

Profiles of patients treated with azithromycin (compared with those treated with clarithromycin) and cefuroxime axetil (compared with those treated with amoxicillin/clavulanate) reveal that the azithromycin- and cefuroxime-treated groups were far more test and procedure intensive without any apparent benefit, as reflected by clinical improvement or response to therapy, but they had a markedly higher overall total cost of care.

In a randomized, prospective trial of macrolides (erythromycin, azithromycin, and clarithromycin), Weiss found a 38% patient dropout rate in patients treated with erythromycin (compared with 8% in the azithromycin and clarithromycin treatment groups). Clinical success rates were very similar in the azithromycin and clarithromycin treatment groups (80% vs 85%, $P < 0.005$), with 40% of the azithromycin treatment group requesting and receiving an antibiotic prescription refill to achieve a positive clinical response to therapy.[84]

The RIMS study demonstrates that the total cost of care for the antimicrobial treatment of sinusitis and bronchitis is affected by the test and procedure intensity associated with specific antibiotics without having an impact on the overall clinical response to therapy. Specific tools can be used and formulary decisions made accordingly to have an effect on the cost of patient care without negatively influencing patient outcomes.

Conclusion

Community-acquired pneumonia and AECB represent significant threats to the health of the US population. The incidence of CAP in the United States reached nearly 5 million cases in 1993, with almost 24% of these patients requiring hospitalization. In 1991, the cost of treating these patients exceeded $5 billion, and associated costs exceeded $7 billion. Chronic bronchitis affects nearly 25% of the US adult population, with many these patients being at risk for acute exacerbations.

Respiratory tract infections represent the single most frequent reason for visiting a healthcare provider. Patient management involves correct diagnosis and careful consideration of empiric- or pathogen-directed antimicrobial therapy. Appropriate patient selection for treatment, the emergence of antimicrobial resistance, the side effects of therapy, compliance issues, and the cost of therapy are major issues facing clinicians in the development of clinical guidelines and pathways to help manage patients with respiratory tract infections.

Streptococcus pneumoniae remains the single most important pathogen in CAP and AECB, accounting for more than 70% of all cases. The increasing resistance of *S. pneumoniae* to penicillin and other drugs is causing clinicians to re-evaluate traditional antimicrobial therapy, because antimicrobial selection must also take into account the significant role of atypical microorganisms such as *C pneumoniae*, *Legionella* sp, and *M. pneumoniae*. Diagnosis of CAP and AECB usually is clinical and roentgenographic, and at present the selection of antimicrobials is most frequently empiric. The role of the PCR

technique on sputum in developing a more widespread and reliable application to permit pathogen-directed therapy remains a promise that has not yet been realized.

The choice of empiric therapy depends on the clinical skill of the physician, taking into consideration coverage and an understanding of the local surveillance data, as well as resistance patterns and a knowledge of the patient's underlying condition, severity of illness, recent hospitalization, residence in an extended care facility, and recent antibiotic use.

Patients with CAP who do not require hospitalization and have a nonproductive cough may begin empiric therapy with a macrolide (clarithromycin or erythromycin) or doxycycline. Exceptions include those with comorbid disease (underlying COPD, diabetes mellitus, congestive heart failure, chronic liver disease, malignancy, substance abuse, hospitalization for CAP within the past year, age older than 60 years, chronic renal failure, and malnutrition).

Such patients are at increased risk of *H. influenzae* and *M. catarrhalis* and should be treated with a second-generation cephalosporin (cefuroxime axetil), amoxicillin clavulanate, clarithromycin, or an advanced-generation fluoroquinolone (sparfloxacin, grepafloxacin, or trovafloxacin). If possible, an etiologic diagnosis should be made and pathogen-directed antibiotic therapy should be instituted.

Patients who are at increased risk of mixed flora pneumonia (aspiration pneumonia) because of altered levels of consciousness; CNS-related bulbar palsy and swallowing reflex abnormalities; head- and neck-related carcinoma; achalasia; residence in an extended-care facility; or colonization of the oropharynx with enteric gram-negative microorganisms related to recent hospitalization should be treated with an advanced-generation fluoroquinolone (trovafloxacin).

Patients with CAP who require hospitalization but are immunocompetent should be treated with a second-generation cephalosporin (cefuroxime) or a third-generation cephalosporin (cefotaxime or ceftriaxone), as well as a macrolide (erythromycin, clarithromycin, or azithromycin). Patients who are at an increased risk of drug-resistant *S. pneumoniae* should be treated with a third-generation cephalosporin (cefotaxime or ceftriaxone), clindamycin, or vancomycin.

The role of fourth-generation fluoroquinolones (sparfloxacin, grepafloxacin, and trovafloxacin) in the treatment of these patients has still to be determined. Although their in vitro activity against DRSP is superior, whether fourth-generation fluoroquinolones offer any clinical advantage over older fluoroquinolones or other types of drugs in this setting has yet to be demonstrated.

With the increased threat of developing vancomycin-related resistance, the drug's use should be reserved for patients who are at increased risk of DRSP, are critically ill, have demonstrated methicillin-resistant *Staphylococcus aureus*, are suspected to have *S. pneumoniae*-related meningitis, or have a documented severe penicillin allergy.

Increasingly, the selection of appropriate antibiotic therapy also involves cost. The RIMS system demonstrates that there are significant cost differences among products of a similar class that do not vary in clinical outcome. Among the second-line products that are routinely used to treat patients with AECB, significant differences in cost have been found, based on test and procedure intensity (cefuroxime/azithromycin> amoxicillin/clavulanate/clarithromycin), whereas patient comorbidity and severity scores were constant, and outcome measures did not differ.

Development of a pathway of cost-effective, appropriate use for antimicrobial selection in patients with CAP and AECB will necessitate a critical look at diagnostic techniques and therapeutic modalities. New products like the fourth-generation fluoroquinolones offer the advantage of an apparently ex-

panded spectrum of activity at a markedly increased cost.

Whether the use of fourth-generation fluoroquinolones in vitro offers superior coverage and translates into any clinical advantage over the use of older fluoroquinolones remains to be demonstrated.

The threat of overusing advanced-generation fluoroquinolones in inappropriate patient subsets and the potential for bacterial overgrowth and resistance cannot be overemphasized. Advanced-generation macrolides continue to offer significant advantages in the treatment of respiratory tract infections secondary to *S. pneumoniae*, *C. pneumoniae*, *Legionella* sp, *M. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. The hallmark of a cost-effective clinical guideline for the treatment of respiratory tract infections rests on its appropriate use.

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