

Bridging the Gap Between Clinical Knowledge and Practical Prevention™

PREVENTIVE MEDICINE

IN MANAGED CARE™

SUPPLEMENT FEBRUARY 2005 • VOL. 5, NO. 1, SUP.

Therapeutic Management of Bronchitis

Jennifer Le, PharmD

Assistant Professor of Pharmacy Practice, College of Pharmacy,
Western University of Health Sciences

Martin S. Lipsky, MD

Dean and Professor of Family Medicine, University of Illinois,
College of Medicine, Rockford

Approved for CME Credit by
UNIVERSITY OF
CINCINNATI
COLLEGE OF MEDICINE

Approved for CE Credit by
MEDICAL WORLD
COMMUNICATIONS
Office of Continuing
Professional Education

By the Publishers of

THE AMERICAN JOURNAL OF
MANAGED CARE

© 2005 Medical World Communications, Inc.

An MWC Publication • Supplement to *The American Journal of Managed Care*

CME Advisor

Kay Weigand

University of Cincinnati, Office of CME

CE Advisor

Emilie McCardell

Medical World Communications
Office of Continuing Professional Education

MWC Publishing Staff

Daniel W. Perkins

Senior VP, Medical/Dental Divisions

Robert Issler

Chief Operating Officer,
Medical and Dental Group

Linda Fox

VP, Primary Care Journals,
Medical Division

Maurice Nogueira

Project Publisher

Lyn Beamesderfer

Group Editorial Director

Colin Gittens

Associate Editorial Director

Jennifer A. Brandt

Assistant Editor

Susan M. Carr

Projects Director

Susan Quinn

Projects Editorial Director

Lara J. Reiman

Associate Projects Editorial
Director

Kimberly A. Melofchik

Assistant Projects Editorial
Director

Barbara Marino

Director, Quality Assurance

Jill Olivero

Copy Editor

Elizabeth Lang

Director, Manufacturing
and Production

Michael S. Hubert

Creative Director

Michael J. Molfetto

Design Director, Projects

Charles Lebeda

Senior Design/
Production Manager

MWC Corporate Officers

John J. Hennessy

Chairman/CEO

Curtis Pickelle

President

Steven J. Resnick

Chief Financial Officer



PUBLISHER'S NOTE: This supplement to *The American Journal of Managed Care*[®] is supported by an unrestricted educational grant from Sanofi-Aventis. The opinions or views expressed in this supplement are those of the author and do not necessarily reflect the opinions or recommendations of Sanofi-Aventis, or the publisher or editors of *The American Journal of Managed Care*[®].

Dosages, indications, and methods of use for compounds that are referred to in this supplement by the authors may reflect their clinical experience or may be derived from the professional literature or other sources. Because of differences between in vitro and in vivo systems and between laboratory animal models and clinical data in humans, in vitro and animal data may not correlate with clinical results and do not demonstrate clinical safety or efficacy in humans. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested by the authors should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturers' product information, and comparison with the recommendations of other authorities.

The American Journal of Managed Care[®] is published monthly by Medical World Communications, Inc., 241 Forsgate Drive, Jamesburg, NJ 08831-0505. Telephone: (732) 656-1140. Copyright © 2005. Medical World Communications, Inc. Printed in the USA. All rights reserved. *The American Journal of Managed Care*[®] is a registered trademark of Medical World Communications, Inc. Periodicals postage is paid at Monroe Township, NJ 08831 and at additional mailing offices. A119

THERAPEUTIC MANAGEMENT of BRONCHITIS

Jennifer Le, PharmD
Assistant Professor of Pharmacy Practice, College of Pharmacy,
Western University of Health Sciences

Martin S. Lipsky, MD
Dean and Professor of Family Medicine, University of Illinois,
College of Medicine, Rockford

Behavioral Objectives

After completing this continuing education article, the pharmacist should be able to:

1. Review the epidemiology and pathogenesis of acute bronchitis, including a discussion of the bacteriologic etiology.
2. Compare and contrast the clinical features of acute (bacterial versus viral) and chronic rhinosinusitis.
3. Discuss the therapeutic options in the treatment of bronchitis.
4. Understand the importance of judicious use of antibiotics in the treatment of bronchitis and the impact of resistance in the development of new drugs and dosage formulations.
5. Formulate a therapeutic plan for a given case study of a patient with acute bronchitis or acute exacerbation of chronic bronchitis.

Acute bacterial bronchitis and acute exacerbation of chronic bronchitis (AECB) are among the most common diseases encountered in clinical practice. Successful treatment can be a challenge, however, especially with the emergence of antibiotic resistance. New agents have been approved by the FDA that address the problem, but society guidelines have yet to catch up with clinical practice. This article will cover therapeutic management of acute bacterial bronchitis and AECB. It also will discuss the challenges of bacterial resistance and ongoing efforts to circumvent this problem.

Acute Bacterial Bronchitis

Acute bronchitis is one of the most common diseases encountered in clinical practice. It is estimated that 30 million ambulatory visits for cough leading to approximately 12 million diagnoses of bronchitis were made in the United States in 1997.¹ Although

viruses are responsible for most cases of acute bronchitis, 70% to 80% of patients with acute bronchitis who seek medical attention are prescribed antibiotics.² Inappropriate prescribing of antibiotics is often the result of physicians meeting the demand and expectations of their patients who insist on such medications for viral infections.

Pathogenesis

Acute bronchitis is defined as inflammation of the bronchi in the presence of cough and associated symptoms of an upper respiratory infection. Some patients may experience dyspnea, purulent sputum production, chest pain, and fever. At least 60% of the time, microbiologic studies are unable to identify a pathogen associated with acute bronchitis.³ As stated above, most identifiable cases of uncomplicated acute bronchitis ($\geq 90\%$) are caused by viruses (Table 1).^{4,5} The

influenza viruses are most frequently associated with acute bronchitis.

Bacterial pathogens account for 5% to 10% of all cases of uncomplicated acute bronchitis.⁵ *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* are the only bacteria that have been associated with acute bronchitis. Although the pertussis vaccine is approximately 90% efficacious, its protective effect in children decreases to 46% in the seventh year after immunization.^{6,7} This decrease creates a large pool of adolescents and adults susceptible to *B pertussis*.

Other bacteria—including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*—do not appear to cause acute bronchitis in adults who do not have underlying lung disease. These bacteria, however, may play a role in secondary infection after an acute viral respiratory illness, or in patients with underlying lung

Table 1^{4,5}

Viruses That Cause Acute Bacterial Bronchitis

- Influenza A and B
- Parainfluenza
- Coronavirus
- Rhinovirus
- Respiratory syncytial virus
- Adenovirus
- Human metapneumovirus

abnormalities (eg, AECBs, tracheostomy, or endotracheal intubation).⁸

Clinical Presentation and Diagnosis

The primary symptom of acute bronchitis is cough (with or without sputum production) lasting less than 3 weeks.⁹ Approximately 20% of patients, however, may continue to experience cough after 4 weeks.¹⁰ *B pertussis* infection should be considered in patients with persistent paroxysmal cough (usually lasting 4-6 weeks) and with close contact with an infected individual.⁵ Approximately 20% of patients with cough lasting longer than 2 to 3 weeks have pertussis.¹¹ The presence of purulent sputum is not exclusive to bacterial causes of acute bronchitis. Purulence can result from either a bacterial or a viral infection.

Diagnosis of acute bronchitis is based on clinical findings and requires excluding the possibility of pneumonia. The absence of abnormal vital signs (heart rate ≥ 100 beats/min, respiratory rate ≥ 24 breaths/min, or oral temperature $\geq 38^\circ\text{C}$) and a normal chest examination significantly decrease the possibility of pneumonia.¹² Chest radiography is recommended for patients with abnormal vital signs or abnormal findings on lung examination, patients with underlying lung disease, and patients with suspected severe acute respiratory syndrome.^{2,3} Postnasal drip syndrome, asthma (especially when the patient is exposed to cold or exercise), gastroesophageal reflux disease, or a combi-

nation of these conditions is the most likely diagnosis in immunocompetent adult patients with persistent cough lasting more than 3 weeks and a negative chest radiograph.^{9,13} In fact, these conditions account for 90% of diagnoses in patients with persistent cough.¹⁴ Because sputum Gram stain and culture do not consistently identify *B pertussis*, *M pneumoniae*, and *C pneumoniae*, these diagnostic tests are not recommended.³

Treatment

The overuse of antibiotics in the treatment of acute bronchitis has been a public health issue over the past decades. Since most cases of uncomplicated acute bronchitis are caused by viruses (Table 1), the routine use of antibiotics—including erythromycin, doxycycline, or trimethoprim/sulfamethoxazole (TMP/SMX)—provides only a marginal benefit and is highly discouraged.^{2,15,16} Hence, antibiotic treatment should not be initiated in patients with acute bronchitis caused by viruses. Despite this caution, physicians prescribe antibiotics for acute bronchitis up to 80% of the time.¹⁶ In addition, the identification of *M pneumoniae* and *C pneumoniae* on culture is difficult. Currently, there is a lack of clinical studies with adequate sample size to support antibiotic treatment for these pathogens.

Guidelines from the American College of Physicians and the Centers for Disease Control and Prevention support the use of antibacterial agents only for bronchitis that is caused by *B pertussis*.^{3,14} Therapy with erythromycin 250 to 500 mg 4 times a day in patients with pertussis helps to resolve symptoms.¹⁷ Other macrolides, including clarithromycin and azithromycin, are therapeutic options for pertussis.

Initiation of treatment early in the course of illness (within 7-14 days after the onset of symptoms) is necessary to maximize the clinical benefit. Patients with pertussis, however, frequently do not seek medical care within this time frame. With these patients, the purpose of recommending antibiotic treat-

ment is to prevent transmission of the disease rather than resolution of symptoms. Antibiotic treatment should be reserved for patients in whom pertussis is highly probable (ie, prolonged cough and recent exposure to a person with pertussis), as well as for their close contacts. Close contacts should be treated with the same dose and duration of erythromycin. Compared with ethylsuccinate and stearate formulations, the estolate formulation of erythromycin has been associated with the fewest bacteriologic and clinical relapses.¹⁸ Hence, estolate is the recommended dosage formulation for the treatment of pertussis. Therapy should continue for 14 days, although a 7-day course has been shown to be equally effective.^{18,19}

Acute bacterial bronchitis caused by atypical pathogens, including *M pneumoniae* or *C pneumoniae*, occurs in a minority of patients. It should be suspected in patients with prolonged cough and bronchial symptoms. Tetracyclines, macrolides, and fluoroquinolones provide excellent activity against these bacteria. Routine use of antibiotics to direct therapy against these pathogens is highly discouraged, however, because there has been a lack of clinical trials to support this practice.

Since patients may present with upper respiratory or common cold symptoms, the use of nasal decongestants, nonsteroidal anti-inflammatory drugs, aspirin, acetaminophen, and/or nasal ipratropium may provide symptomatic relief. Because most cases of acute bronchitis present with cough, antitussives, such as dextromethorphan and codeine, to reduce cough are often prescribed, although the evidence supporting their benefit is small.⁵ A recent meta-analysis concluded that the use of oral or inhaled beta-2 agonists was not effective in reducing acute cough in adults and children who did not have airflow obstruction.²⁰

Acute Exacerbation of Chronic Bronchitis

Chronic bronchitis, particularly during acute exacerbation, contributes to

significant disability, morbidity, and mortality in people with chronic obstructive pulmonary disease (COPD). In the United States, approximately 16 million people are affected by COPD.²¹ Evidence indicates that COPD, particularly its mild form, is underdiagnosed.²² AECB has been shown to impair the quality of life of people with COPD.²³ An estimated 500,000 hospitalizations and 110,000 deaths occur annually in patients with COPD exacerbations.^{21,22} The World Health Organization in 2002 reported that COPD was the fifth leading cause of death in the world, and its prevalence and mortality are predicted to increase.^{24,25} Because the prevalence is high, the economic and social impact of COPD is considerable. The annual expenditure for COPD is \$23.9 billion, with an estimated direct cost of \$1500 per patient per year.^{26,27}

Pathogenesis

Chronic bronchitis is characterized by increased mucosal inflammation and mucus hypersecretion of the bronchi, and it usually is accompanied by airflow obstruction. Smoking is associated with most cases of COPD. Air pollution, allergens, occupational exposure, airway infection, and genetic factors (eg, deficiency in alpha₁-antitrypsin) are also risk factors for COPD.²⁷ AECB is characterized by an increase in the quantity and purulence of sputum, increased dyspnea, and fever. Although inhaled irritants, pollution, and allergies can trigger an acute exacerbation, infections caused by viruses and bacteria account for 50% to 80% of AECB cases.^{28,29} Viruses—including influenza, rhinovirus, parainfluenza, respiratory syncytial virus, coronavirus, and adenovirus—contribute to the majority (33%-56%) of AECB cases.²⁹⁻³²

The most common bacterial pathogens isolated in patients with AECB are *S pneumoniae*, *H influenzae*, and *M catarrhalis*.³³ *C pneumoniae*, *M pneumoniae*, *Staphylococcus aureus*, *Klebsiella*, and *Pseudomonas aeruginosa* also may cause AECB.^{28,30,34} Interestingly, bacte-

ria that are isolated in patients with stable chronic bronchitis are similar to ones that are cultured during acute exacerbations.²⁹ Patients with chronic bronchitis usually are colonized with bacteria, which may cause and lead to airway inflammation.^{35,36}

Clinical Presentation and Diagnosis

Chronic bronchitis is characterized by persistent cough and sputum production for 3 months per year for at least 2 consecutive years. Patients with AECB present with more frequent and/or severe symptoms of COPD, as well as other features (Table 2).

Chest radiography remains unchanged during AECB and is useful to differentiate AECB from pneumonia, because the clinical presentations may be similar. Expecterated sputum samples of patients with COPD contain a high concentration of polymorphonuclear leukocytes (PMNs), both during stable chronic bronchitis and AECB.³⁷ As noted earlier, pathogens cultured during stable chronic bronchitis are similar to those of AECB. The indistinct pattern of bacteria and PMNs between stable bronchitis and AECB makes sputum cultures of little value in diagnosing AECB. In fact, the American College of Physicians does not recommend performing sputum cultures during exacerbations.²¹ Sputum cultures should be reserved for patients not responding to empirical antibiotic therapy.

Treatment

Clinically significant AECB is more likely to occur in patients with bacterial colonization and severe underlying pulmonary disease. In this patient population, AECB may lead to hospitalization and respiratory failure. Hence, antibiotic treatment should be offered for eradication of bacteria and resolution of airway inflammation.³⁶ Mild episodes of AECB, especially in patients with less severe underlying lung disease (forced expiratory volume in 1 sec >50% of predicted value), may resolve spontaneously, and judicious use of antibiotics in this population is merited to prevent bacterial resistance.

Table 2

Features of AECB

- Cough
- Dyspnea
- Sputum production
- Purulence
- Increased respiratory rate (>25 breaths/min)
- Decreased pulmonary function (forced expiratory volume in 1 sec)
- Constitutional symptoms

AECB = acute exacerbation of chronic bronchitis.

Studies evaluating the use of antibiotics in patients with AECB, identified by worsening dyspnea and increased purulence and volume of phlegm, demonstrated clinical benefit.³⁸⁻⁴⁰ Antibiotics were beneficial in patients with 2 of these 3 symptoms, but appeared to offer minimal or no benefit in patients with mild exacerbations (ie, when only 1 or none of these symptoms were present). Based on recommendations from the American College of Chest Physicians, the National Institutes of Health, and the American Thoracic Society, empirical antibiotic therapy directed against the common bacterial pathogens of AECB is recommended for patients with AECB, especially if infection is severe.^{21,41,42} The choice of antibiotic should reflect local susceptibility patterns of *S pneumoniae*, *H influenzae*, and *M catarrhalis*. A narrow-spectrum antibiotic (eg, amoxicillin 500 mg 3 times daily, doxycycline 100 mg twice daily, or TMP/SMX 160/800 mg twice daily) for 3 to 14 days generally is used.^{21,41,43} The optimal duration of therapy has not been well-studied. Unfortunately, the increasing prevalence of resistance among the common bacterial pathogens of AECB, particularly in patients with severe underlying COPD or those with recent antibiotic usage, limits the effectiveness of these narrow-spectrum agents.

New Approaches to Treatment of AECB

New or extended-spectrum antibiotics have been studied or FDA-

Table 3^{33,44}**New or Extended-Spectrum Antibiotics for the Treatment of AECB**

- Amoxicillin with clavulanate
- Cephalosporins
- Respiratory fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin, and gemifloxacin)
- Macrolides (clarithromycin and azithromycin)
- Telithromycin

AECB = acute exacerbation of chronic bronchitis.

approved for the treatment of AECB (Table 3).^{33,44} These antibiotics may play a major role in the treatment of AECB. In fact, studies have demonstrated that the use of these new or extended-spectrum antibiotics, compared with the use of the traditional narrow-spectrum agents, was associated with fewer relapses.^{44,45} For the past 3 years, however, there have been no updates of guidelines from major authorities to help direct physicians on the appropriate use of these new antimicrobials as first-line agents.

High-dose amoxicillin with clavulanate is now available in formulations intended to enhance compliance and effectiveness against drug-resistant *S pneumoniae* (1000 mg amoxicillin and 62.5 mg clavulanate per extended-release tablet; 14:1 ratio of amoxicillin to clavulanate in powder for oral suspension). Amoxicillin (\pm clavulanate), which exerts its bactericidal activity by inhibiting cell-wall synthesis, remains as a first-line therapeutic option for treating AECB. The clavulanate component provides additional activity against beta-lactamase producers, *H influenzae* and *M catarrhalis*.

Pharmacokinetic and pharmacodynamic studies demonstrate that *high-dose* amoxicillin (\pm clavulanate), defined as 4 g per day in adults, provides enhanced activity against resistant pneumococci.^{46,47} The most common adverse effects are gastrointestinal-related, including nausea and diarrhea. The incidence of adverse effects associ-

ated with high-dose amoxicillin is comparable to that with standard-dose amoxicillin.^{47,48} Compared with twice-daily dosing, however, 3-times-daily dosing of high-dose amoxicillin was associated with a significantly higher incidence of diarrhea.⁴⁶

Fluoroquinolones bind to enzymes, including DNA gyrase and topoisomerase IV to inhibit bacterial DNA synthesis. Major advantages of this class of antibiotics are their excellent penetration into respiratory secretions and infrequent dosing. In addition, the fluoroquinolones provide excellent coverage against most respiratory pathogens, including atypical bacteria (eg, *C pneumoniae* and *M pneumoniae*). Only a minute number of cases of AECB and acute bronchitis are caused by atypical bacteria, however. Levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin, which have been available for a number of years, provide excellent activity against *S pneumoniae*, *H influenzae*, *M catarrhalis*, and *S aureus* and are FDA-approved for the treatment of AECB.⁴⁹ Ciprofloxacin, although active against *H influenzae* and *M catarrhalis*, has limited activity against pneumococci. Although fluoroquinolones are increasingly used for treating AECB, the recent emergence of pneumococci with reduced susceptibility to fluoroquinolones has created concern about their widespread usage.⁵⁰⁻⁵²

The newer macrolides, including clarithromycin and azithromycin, also provide excellent activity against *S pneumoniae*, *H influenzae*, and *M catarrhalis* as well as against atypical respiratory pathogens. Macrolides exert their bacteriostatic activity by binding to the 50S ribosomal subunit to inhibit protein synthesis. The FDA recently approved the extended-release formulation of clarithromycin for once-daily dosing to enhance compliance. Fluoroquinolones and macrolides are therapeutic options for patients with true hypersensitivity to penicillin. They have been associated with emerging resistance, however, particularly among penicillin-nonsusceptible pneumococcal isolates in the United States.^{51,53,54}

A new class of antibiotics called the ketolides was developed to address macrolide-resistant bacteria.⁵⁵ In the presence of the *ermB* gene (and, in the case of telithromycin, *ermB* and *meFA* genes), ketolides remain active against macrolide-resistant pathogens.⁵⁶ Although similar to the macrolides, ketolides bind more tightly to the 50S ribosomal subunit to enhance their activity against respiratory pathogens resistant to macrolides.⁵⁷ Telithromycin, the first ketolide, recently received FDA approval for the treatment of AECB, acute bacterial rhinosinusitis, and mild-to-moderate community-acquired pneumonia. The spectrum of activity of telithromycin in the treatment of AECB includes *H influenzae*, *M catarrhalis*, *S pneumoniae*, *S aureus*, *C pneumoniae*, and *M pneumoniae*.⁵⁸ Telithromycin 800 mg once daily for 5 days provided a clinical cure rate of 78% to 86%, which is comparable to comparators cefuroxime and amoxicillin/clavulanate.^{59,60} The 5-day regimen also offers improved ease of administration as compared with the standard 10-day regimens of amoxicillin/clavulanate, cefuroxime, and clarithromycin. Telithromycin serves as an alternative in the treatment of AECB. The most common adverse effects reported were gastrointestinal-related, including nausea and diarrhea. A case report noting the potential for interaction between telithromycin and warfarin suggests that until further information is available, those patients on warfarin and telithromycin therapies should be closely monitored.

Other treatment considerations for patients with AECB and COPD are antibiotic prophylaxis, mucolytic agents, and vaccines. Antibiotics, specifically tetracycline or TMP/SMX, for patients with chronic bronchitis should not be routinely used prophylactically, because the benefit is limited to a minor reduction in the number of days of illness from AECB.⁵⁹ If used, antibiotic prophylaxis, particularly during the winter months, should be considered only for patients with mul-

Table 4

Antibiotic Mechanisms of Action and Bacterial Resistance Among Respiratory Pathogens

Antibiotic Class	Mechanism of Action	Mechanism of Bacterial Resistance
Beta-lactams	Interfere with synthesis of bacterial cell wall	<ul style="list-style-type: none"> • Alteration of the target proteins that are key to bacterial wall assembly • Destruction of beta-lactam ring by production of beta-lactamase enzymes
Macrolides	Inhibit synthesis of proteins by binding to bacterial 50S ribosomes	<ul style="list-style-type: none"> • Methylation of a ribosomal RNA binding site (<i>ermB</i>) • Decrease of antibiotic accumulation by efflux pumps (<i>mefA</i>)
Ketolides	Inhibit ribosomal assembly and also inhibit protein synthesis by tightly binding to bacterial 50S ribosomes	<ul style="list-style-type: none"> • Less vulnerable to bacterial resistance mechanisms than related macrolides
Fluoroquinolones	Inhibit synthesis of bacterial DNA by binding to DNA gyrase and topoisomerase IV	<ul style="list-style-type: none"> • Mutation of antibiotic target enzymes, thus lowering drug affinity for these proteins

multiple relapses of AECB within a year.

In a recent meta-analysis, treatment with mucolytics has been shown to reduce acute exacerbations and the total number of days of disability.⁶¹ Influenza and pneumococcal vaccines are recommended for patients with COPD and other chronic lung diseases. Annual administration of the influenza vaccine reduces the rate and severity of illness, lost workdays, and physician visits.⁶² The polysaccharide pneumococcal vaccine appears to reduce invasive pneumococcal disease.⁶³

Challenges of Bacterial Resistance

Bacterial resistance among respiratory pathogens occurs through multiple mechanisms (Table 4). Over the past few decades, antibiotic resistance has increased dramatically. To address resistance, the most recent guidelines for the treatment of acute bronchitis and AECB focus on judicious use of antibiotics. Under the selective pressure of antibiotic use, susceptible bacteria succumb, and, with less competition, resistant bacteria flourish. William Osler once wrote that the desire to take medicine is perhaps the greatest feature that distinguishes humans from animals. This desire appears to be especially true for antibiotics. Their overuse greatly contributes

to the increasing trend of resistance among respiratory bacterial pathogens. For example, *multidrug-resistant pneumococci*, defined as strains resistant to at least 3 classes of antibiotics, were recovered in 26% of all isolates.⁵¹

The most common bacterial pathogens associated with AECB are *S pneumoniae*, *H influenzae*, and *M catarrhalis*. Alteration of the penicillin-binding proteins, a resistance mechanism acquired by pneumococci, renders the organisms resistant to penicillins, cephalosporins, and other beta-lactam antibiotics. In the United States, the prevalence of penicillin-nonsusceptible (include resistant and intermediately susceptible) strains of *S pneumoniae* reached a peak of 36% in 2001.⁶⁴ In addition, penicillin-nonsusceptible strains of *S pneumoniae* are associated with cross-resistance to other classes of antibiotics. Thus these isolates are termed *drug-resistant S pneumoniae* (DRSP). Resistance of DRSP to other antibiotics includes TMP/SMX (37%), macrolides (29%), doxycycline (21%), clindamycin (10%), and ofloxacin (7%).⁵³ Most isolates of *S pneumoniae* remain susceptible to respiratory fluoroquinolones (including gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin). Concern about the development of resistance is arising, however, from the extensive use of fluoro-

quinolones in the treatment of community-acquired respiratory tract infections.⁵⁰

Cross-resistance between erythromycin and clindamycin occurred in approximately 32% of *S pneumoniae* isolates in the United States.⁵³ Resistance to both erythromycin and clindamycin is mediated by the *ermB* ribosomal methylation mechanism (MLS_B-phenotype), which inhibits binding of the antibiotic to the target site.^{64,65} Most erythromycin-resistant *S pneumoniae* strains (68%) remain susceptible to clindamycin, however.⁶⁶ In these isolates, resistance occurs by the *mefA* efflux pump (M-phenotype), which decreases antibiotic accumulation in the bacteria.^{66,67}

H influenzae (30%) and *M catarrhalis* (92%) confer resistance to penicillins by producing beta-lactamases.⁵³ Beta-lactamase-inhibitor combinations (eg, amoxicillin with clavulanate) and cephalosporins (specifically, ceftriaxone, cefixime, and cefdinir) retain excellent activity against these pathogens. Both *H influenzae* and *M catarrhalis* are highly susceptible to the fluoroquinolones. Resistance of *H influenzae* to TMP/SMX (22%) has been observed.⁵⁵

Many studies strongly suggest that judicious use of antibiotics reduces resistance. In Finland, for example, a

Table 5

Strategies to Reduce Antibiotic Use

Prevention of infections by:
Proper hand washing
Annual flu vaccination

Use of symptomatic treatments

Avoidance of use of antibiotics for viral infections

Patient education

Public campaigns

Encourage physicians to resist over-prescribing antibiotics

campaign to restrict antibiotic use led to a decrease in erythromycin resistance among Group A streptococci.⁶⁸ This outcome supports the concept

that a thoughtful approach to the use of antibiotics and restricting their use to appropriate situations will be beneficial. Table 5 provides some strategies to reduce antibiotic use.

Conclusion

To optimize the treatment of acute bronchitis and AECB, the clinician must understand the pathogenesis and clinical features of these infections. Viruses are responsible for most cases of acute bronchitis and AECB. In these scenarios, routine use of antibiotics is inappropriate and highly discouraged, because it may contribute to the increasing prevalence of bacterial resistance. To encourage judicious use

of antibiotics, the clinician must determine when bacterial infection is highly probable. Furthermore, although it is critical to consider guidelines when selecting the optimal therapy, new research demonstrates improved treatment in cases of bacterial resistance, and the society guidelines have yet to catch up with clinical practice. ^{PT}

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: astahl@mwc.com.

Case Study

A 65-year-old man presents to a primary care clinic with a marked increase in cough and purulent sputum production for the past 4 days. He reports experiencing a fever of 38.5°C and worsening dyspnea since 2 days ago. He has a history of diabetes mellitus, chronic bronchitis, and severe COPD. The patient is currently taking several medications for his lung disease and has been compliant with his regimen. Two weeks ago, he received TMP/SMX for the treatment of a urinary tract infection. The result of a chest x-ray, which was done to exclude pneumonia, indicates chronic lung changes with no acute infiltrate. What are treatment considerations for this patient diagnosed with severe AECB?

AECB is characterized by an increase in the frequency and/or severity of symptoms associated with COPD, including cough, dyspnea, and sputum production and purulence. These symptoms, accompanied by fever, are present in this patient. Because symptoms of AECB may overlap with those associated with pneumonia, pneumonia must be considered in the differential diagnosis, particularly in this patient with chronic lung disease. The chest x-ray revealed no acute changes; hence, this patient was diagnosed with AECB.

Although viruses contribute to the majority of cases of AECB, bacterial pathogens—most commonly *S pneumoniae*, *H influenzae*, and *M catarrhalis*—also can cause AECB. Antibiotic treatment should be reserved for patients with clinically significant AECB, which is more likely to occur when multiple symptoms associated with AECB and severe underlying pulmonary disease are present. Therefore, antibiotic therapy is recommended for the case patient with severe underlying COPD who is experiencing increased and worsening symptoms. The goals of therapy are to (1) resolve symptoms associated with airway inflammation, (2) eradicate bacteria, (3) prevent hospitalization, and (4) prevent complications, including respiratory distress and/or failure.

Therapeutic options for the treatment of AECB include a narrow-spectrum antibiotic (eg, amoxicillin, doxycycline, or TMP/SMX). With the recent exposure to TMP/SMX, however, there is a higher likelihood of infection caused by a resistant pathogen, specifically *S pneumoniae* or *H influenzae*. In addition, the increasing prevalence of bacterial resistance in patients with severe underlying COPD limits

the effectiveness of these narrow-spectrum agents.

New or extended-spectrum antibiotics that have been studied or FDA-approved for the treatment of AECB are amoxicillin with clavulanate, cephalosporins, respiratory fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin, and gemifloxacin), macrolides (clarithromycin and azithromycin), and telithromycin. Although these antimicrobial agents, as compared with the narrow-spectrum antibiotics, have been associated with fewer relapses, there have been no updates of guidelines from major authorities to help direct physicians on the appropriateness of their use as first-line agents. Nonetheless, these are therapeutic options in the case patient. One major advantage of fluoroquinolones, macrolides, and telithromycin is that they provide excellent activity against atypical bacteria (eg, *C pneumoniae* and *M pneumoniae*), which are less common causes of AECB. In addition to antibiotic therapy, treatment for the case patient's COPD should be optimized. He also should receive a mucolytic agent and influenza and pneumococcal vaccines.

THERAPEUTIC MANAGEMENT OF BRONCHITIS

Choose the 1 most correct answer.

1. What percentage of uncomplicated acute bronchitis is caused by bacterial pathogens?
 - a. 5% to 10%
 - b. 10% to 15%
 - c. 15% to 20%
 - d. 20% to 25%
2. What is the primary symptom presented by a patient with acute bronchitis?
 - a. Fever lasting less than 3 weeks
 - b. Fever lasting more than 3 weeks
 - c. Cough lasting less than 3 weeks
 - d. Cough lasting more than 3 weeks
3. A 22-year-old college student presents shortly after Christmas vacation with a 4-day history of a productive cough, myalgias, and a low-grade fever. Several of her classmates have similar symptoms. The most likely cause of her infection is:
 - a. *Mycoplasma pneumoniae*.
 - b. *Chlamydia pneumoniae*.
 - c. Coronavirus.
 - d. Influenza virus.
4. Diagnosis of acute bronchitis is based on clinical findings and requires the exclusion of pneumonia. Chest radiography may help exclude pneumonia. In which of the following scenarios is the use of chest radiography appropriate?
 - a. In a patient with the following vital signs: heart rate 80 beats/min, respiratory rate 20 breaths/min, and oral temperature <38°C
 - b. In a patient with suspected pertussis
 - c. In a patient with underlying lung disease
 - d. In a patient with a history of persistent cough and purulent sputum production for 2 weeks
5. The routine use of antibiotics in the treatment of acute bronchitis is not recommended, because viruses account for the majority of cases. Which of the following pathogens is most likely to cause you to consider using an antibiotic for the treatment of acute bronchitis in a patient without underlying lung disease?
 - a. *Streptococcus pneumoniae*
 - b. *C pneumoniae*
 - c. *M pneumoniae*
 - d. *Bordetella pertussis*
6. Patients with pertussis generally seek medical care later in the course of infection. What is the primary purpose for recommending antibiotic treatment in these patients?
 - a. Antibiotic therapy can prevent transmission.
 - b. Antibiotic therapy can prevent complications.
 - c. Antibiotic therapy can resolve symptoms.
 - d. Antibiotic therapy is not indicated, because pertussis is a self-limiting infection.
7. What is the oral formulation of erythromycin recommended for the treatment of acute bronchitis caused by *B pertussis*?
 - a. Ethylsuccinate
 - b. Estolate
 - c. Stearate
 - d. Lactobionate
8. Which of the following antibiotics is active against atypical bacterial pathogens including *M pneumoniae* and *C pneumoniae*?
 - a. High-dose amoxicillin
 - b. Amoxicillin with clavulanate
 - c. Levofloxacin
 - d. Clindamycin
9. Which of the following infections contributes to significant disability, morbidity, and mortality in people with chronic obstructive pulmonary disease?
 - a. Acute bacterial rhinosinusitis
 - b. Chronic rhinosinusitis
 - c. Acute bronchitis
 - d. Chronic bronchitis
10. Chronic bronchitis is characterized by increased mucosal inflammation and mucus hypersecretion. What is the most common cause of acute exacerbation of chronic bronchitis (AECB)?
 - a. Smoking
 - b. Virus
 - c. Bacteria
 - d. Air pollution or allergen
11. An AECB is characterized by all of the following *except*:
 - a. An increase in sputum production.
 - b. Increasing cough.
 - c. An abnormal chest x-ray.
 - d. Dyspnea.
12. A 70-year-old woman presents to the hospital with increased cough and sputum production. She also complains of worsening dyspnea and labored breathing (respiratory rate, 26). Gram staining of her sputum sample reveals many polymorphonuclear leukocytes (PMNs). Which of the following clinical features is least consistent with AECB?
 - a. Expectorated sputum containing many PMNs
 - b. Increased frequency and severity of cough and sputum production
 - c. Increased respiratory rate (>25 breaths/min)
 - d. Worsening dyspnea
13. For which of the following patients would you recommend collecting a sputum sample for Gram stain and culture?
 - a. A patient with AECB who is not responding to empirical antibiotic therapy
 - b. A patient with acute bronchitis caused by *M pneumoniae*
 - c. A patient with persistent and paroxysmal cough lasting 3 weeks
 - d. A patient with purulent cough for 3 months in 2 consecutive years
14. Which of the following antibiotics is considered a narrow-spectrum antibiotic used in the treatment of acute exacerbations of chronic bronchitis?
 - a. Levofloxacin
 - b. Amoxicillin
 - c. Azithromycin
 - d. Clarithromycin
15. High-dose amoxicillin with clavulanate has enhanced activity against which of the following bacterial pathogens?
 - a. *M pneumoniae*
 - b. Drug-resistant *S pneumoniae*
 - c. *Moraxella catarrhalis*
 - d. b and c only
16. Twice-daily dosing of high-dose amoxicillin, compared with 3-times-daily dosing, has been associated with a signif-

icantly lower incidence of _____.

- a. Nausea
- b. Diarrhea
- c. Rash
- d. Hypersensitivity reaction

17. What is the primary concern with the use of fluoroquinolones in the treatment of AECB?

- a. Poor penetration into respiratory secretions
- b. Frequent dosing
- c. Emergence of resistance
- d. Inadequate coverage against atypical bacterial pathogens

18. Which of the following antibiotics exerts its effect by binding tightly to the

50S ribosomal subunit to enhance activity against respiratory pathogens, including drug-resistant *S pneumoniae*?

- a. Amoxicillin
- b. Clarithromycin
- c. Moxifloxacin
- d. Telithromycin

19. Isolates of *S pneumoniae* may harbor antibiotic resistance mediated by the *ermB* ribosomal methylation mechanism. To what antibiotics are these strains resistant?

- a. Erythromycin and clindamycin
- b. Amoxicillin and doxycycline
- c. Fluoroquinolones and cephalosporins
- d. Trimethoprim/sulfamethoxazole

20. How does *Haemophilus influenzae* confer resistance to penicillins?

- a. Ribosomal methylation mechanism
- b. Production of beta-lactamases
- c. Alteration of penicillin-binding protein
- d. Efflux pump

CME INSTRUCTIONS (FOR PHYSICIANS)

TESTING AND GRADING PROCEDURES

1. Each participant achieving a passing grade of 70% or higher on any examination will receive an official computer form stating the number of CME credits earned. This form should be safeguarded and may be used as documentation of credits earned.
2. Participants receiving a failing grade on any exam will be notified and permitted to take one reexamination at no cost.
3. All answers should be recorded on the answer form. Please print clearly to ensure receipt of CME credit.
4. Detach and mail or fax your completed exam form to: University of Cincinnati, Office of CME, P.O. Box 670567, Cincinnati, OH 45267-0567; phone: 513-558-7277; fax: 513-558-1708.

Please photocopy the test form for additional test takers.

**The American Academy of Physician Assistants
accepts AMA category 1 CME credit for the PRA
from organizations accredited by ACCME.**



The University of Cincinnati College of Medicine designates this educational activity for a maximum of 2.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours that he/she actually spends in the educational activity.

The University of Cincinnati College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor medical education for physicians.

CE INSTRUCTIONS (FOR PHARMACISTS)

TESTING AND GRADING PROCEDURES

- Each participant achieving a passing grade of 70% or higher on any examination will receive a statement of credit giving the number of CE credits earned. This form should be safeguarded and may be used as documentation of credits earned.
- Participants receiving a failing grade on any exam will be notified and permitted to take 1 reexamination at no extra cost.
- All answers should be recorded on the answer form attached. For each question, decide which choice is the best answer, and circle the letter of the response representing your choice.
- Mail your completed exam form to the following address: Pharmacy Times, 405 Glenn Drive, Suite 4, Sterling, VA 20164-4432.

NEW SCORING OPTIONS

- Mail
- Fax: 703-404-1801
- This lesson is **FREE** on-line; receive instant grading, as well as download your certificate—www.pharmacytimes.com

Please print clearly—certificate will be issued from information given.

Please mail completed forms to:
Pharmacy Times CE Department, 405 Glenn Drive,
Suite 4, Sterling, VA 20164-4432



MWC Office of Continuing Professional Education is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is approved for 2.5 contact hours (0.25 CEU) under the ACPE universal program number of 290-999-05-002-H01. The program is available for CE credit through February 28, 2008.

THERAPEUTIC MANAGEMENT of BRONCHITIS

CME/CE ANSWER FORM

- | | | |
|------------|-------------|-------------|
| 1. a b c d | 8. a b c d | 15. a b c d |
| 2. a b c d | 9. a b c d | 16. a b c d |
| 3. a b c d | 10. a b c d | 17. a b c d |
| 4. a b c d | 11. a b c d | 18. a b c d |
| 5. a b c d | 12. a b c d | 19. a b c d |
| 6. a b c d | 13. a b c d | 20. a b c d |
| 7. a b c d | 14. a b c d | |

(PLEASE PRINT CLEARLY)

SSN -- (Pharmacists ONLY)

Name _____

Address _____

City _____

State _____ Zip _____ Daytime Phone _____

PROGRAM EVALUATION

Please mark your level of agreement with the following statements. (4 = Strongly Agree; 0 = Strongly Disagree)

- | | | | | | |
|------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1) Met its stated objectives | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2) Was well organized | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3) Contributed to my knowledge | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4) Presented current and relevant information | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5) Presented information in a fairly balanced and noncommercial manner | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6) Offered information useful in my professional practice | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7) Provided new insights into contemporary pharmacy practice | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |



