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The Practical Journal for Emergency Physicians

Emergency Medicine Reports®

Volume 24, Number 23

November 3, 2003

Appropriate and Outcome-Effective Antibiotic Use in Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB)

The SCMARTI (Selection of Cephalosporins, Macrolides, and AFQs for Respiratory Tract Infections) Clinical Consensus Panel Report®—Landmark Series In Antibiotic Management: Year 2003 Update—Part II

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—On behalf of the SCMARTI Clinical Consensus Panel

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Antibiotic drug selection for acute bacterial exacerbations of chronic bronchitis (ABECB) requires selecting among a number of available antimicrobials and using such agents in appropriately risk-stratified patients. Certain agents offer the advantages of short-course therapy, while other antibiotics provide expanded coverage to include gram negative organisms that may be encountered in patients with more extensive structural disease and a history of colonization with Pseudomonas species. As a rule, antibiotics with an extremely broad spectrum of coverage (i.e., levofloxacin) should be restricted to those 10-15% of risk-stratified ABECB patients known to be at risk for bacterial exacerbation caused by gram negative organisms encountered in patients at the more severe spectrum of this disease. For the overwhelming majority of patients of ABECB, short-course therapy with agents (i.e., moxifloxacin or azithromycin) with activity against S. pneumoniae*,* H. influenzae*, and* M. catarrhalis*, represents an evidence-based approach to optimizing outcomes.*

In this second part of our two-part series, the SCMARTI Panel recommendations for antimicrobial therapy in ABECB are presented, along with a comprehensive treatment table to guide therapy in the emergency department and outpatient setting.

—The Editor

Antibiotic Therapy for ABECB: The SERF (Severity of Exacerbation and Risk Factor) Pathway for Outcome-Effective Drug Selection

Patients in whom exacerbation of chronic obstructive pulmonary disease (COPD) is associated with acute respiratory

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infection are at high risk for relapse unless treated.[1] Patients with acute bronchitis that is unrelated to COPD probably do not benefit from antibiotic therapy. It should be noted, however, that for patients with COPD, antibiotics appear to have a role in the treatment of exacerbations caused by bacterial bronchitis (i.e., ABECB).[2,3] The outpatient with an increase in sputum quantity and/or a change in character or color, especially if accompanied by increasing cough and dyspnea, should be treated with a course of outpatient antibiotics.

It should be stressed that many patients with COPD have colonization of their tracheal tract with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*.[4] Other organisms, such as Klebsiella species, *Mycoplasma pneumoniae*, Pseudomonas, *S. aureus*, Proteus species, or Chlamydia TWAR also may be seen. Unfortunately, making an etiologic bacteria-specific diagnosis in ABECB usually is not possible. Consequently, most patients will require empiric therapy directed toward the most likely etiologic organisms.

Although a number of clinical decision support tools, consensus guidelines, and recommendations have been issued, none has universal support. In large part, this is because the etiologic agents responsible for ABECB, the outcome-effectiveness of various antibiotics, and risk-stratification parameters are not as thoroughly elaborated as they are for community-acquired pneumonia (CAP). Consequently, several authors have argued that there is an immediate need for guidelines on antibiotic use in COPD.[2,3,7]

The SCMARTI Clinical Consensus Panel has reviewed published trials and generated a set of guidelines based on evidence-based trials. (*See Table 1.*) Several attempts to formulate such protocols have resulted in broadly similar recommendations. Although the guidelines inevitably have been hampered by the lack of well-designed prospective studies, they have taken a practical approach that seems to be logical and can be used in the emergency medicine and primary care settings. It must be emphasized, however, that the concepts on which the guidelines are based have not yet been verified by prospective clinical trials.[5,6,7]

Antibiotic Options. A number of relatively inexpensive, well-tolerated antibiotics are available for treatment of ABECB, including amoxicillin, trimethoprim-sulfamethoxazole, doxycycline, and tetracycline. Antimicrobial resistance, particularly involving *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*, has become an increasing problem with members of each of these drug classes. There is an increase in amoxicillin-resistant, beta-lactamase-producing *H. influenzae*. New agents are providing solutions to these difficulties. The azalide antibiotic azithromycin has the advantage of an appropriate spectrum of coverage, an acceptable safety profile, reasonable cost, and a three-day dosing schedule that may improve patient compliance.

The newer fluoroquinolones (moxifloxacin, gatifloxacin, and levofloxacin) are advantageous when gram-negative bacteria predominate. Ciprofloxacin can be considered for this subgroup, especially in those with structural lung disease such as bronchiectasis and documented infection with gram-negative species (e.g., Pseudomonas species). Its use is discouraged when *S. pneumoniae* infection is suspected. Amoxicillin-clavulanate also has in vitro activity against beta-lactamase-producing *H. influenzae* and *M. catarrhalis*, as well as *S. pneumoniae*; moreover, the agent's clinical efficacy in lower respiratory tract infection (RTI) attributable to enzyme-producing strains has been demonstrated.

Severity of Exacerbation and Risk Factors Pathway. The Severity of Exacerbation and Risk Factors (SERF) pathway for antibiotic selection in outpatients with acute bacterial exacerbations of chronic obstructive lung disease (ABE/COPD) is a clinical decision, consensus-driven support tool based on epidemiolo-

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

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

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In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Stapczynski (peer reviewer) reports no relationships with companies related to the field of study covered by this CME program. Dr. Volturo (author) is on the speaker's bureau for Pfizer and Scios and receives research grants from Roche. Dr. Emerman (peer reviewer) is a consultant for Scios and Aventis; is on the speaker's bureau for Scios, Pfizer, Roche, and Bayer; and conducts research for Scios and Aventis. Dr. Bosker (author and editor) is on the speaker's bureau for Pfizer, Rhone-Poulenc Rorer, and Parke-Davis. Dr. Bosker also acknowledges that he receives royalties, commissions, and other compensation relating to the sale of textbooks, reprints of articles, and other written materials to the following pharmaceutical companies: Pfizer, Genentech, Aventis, Pharmacia, and Bayer.

Table 1. Outpatient Management of Bacterial Infections in the Lower Respiratory Tract (OMBIRT) Panel Treatment*† Guidelines[9] Endorsed by SCMARTI Clinical Consensus Panel

SERF CATEGORY A**

CONDITION • SEVERITY • SUSPECTED PATHOGENS

Acute Bacterial Exacerbation of COPD (ABE/COPD)
Mild severity based on SERF (severity of exacerbation and risk factors) pathway and IOTT (intensity of treatment triggers) criteria
— Suspected pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*

Initial (preferred agent, any class) first-line therapy: Azithromycin 500 mg PO qd x 3 days
Initial (preferred AFQ): Moxifloxacin 400 mg PO qd x 5 days
Alternative first-line agents (macrolides): Clarithromycin 500 mg PO qd x 7 days
Alternative first-line agents (fluoroquinolones): Gatifloxacin 400 mg PO qd x 7 days; Levofloxacin 500 mg PO qd x 7 days
Alternative first-line agents (other classes, including generic formulations): Amoxicillin-clavulanate 875 mg PO q 12 hours x 10 days; Doxycycline 100 mg PO bid x 7-14 days; Trimethoprim-sulfamethoxazole 1 DS tablet PO bid x 7-14 days

SERF CATEGORY B

CONDITION • SEVERITY • SUSPECTED PATHOGENS

Moderate-to-severe bacterial exacerbation of COPD (ABE/COPD)
Severity based on SERF (severity of exacerbation and risk factors) pathway and IOTT (intensity of treatment triggers) criteria
— Suspected pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*

Initial (preferred agent, any class) first-line therapy: Azithromycin 500 mg PO qd x 3 days
Initial (preferred AFQ): Moxifloxacin 400 mg PO qd x 5 days
Alternative first-line agents (macrolides): Clarithromycin 500mg PO qd x 7 days
Alternative first-line agents (fluoroquinolones): Gatifloxacin 400 mg PO qd x 7 days; Levofloxacin 500 mg PO qd x 7 days
Alternative first-line agents (other classes): Amoxicillin-clavulanate 875 mg PO q 12 hours x 10 days

SERF CATEGORY C

CONDITION • SEVERITY • SUSPECTED PATHOGENS

Severe and/or frequently recurrent bacterial exacerbation of COPD (ABE/COPD)
Severity based on SERF (severity of exacerbation and risk factors) pathway and IOTT (intensity of treatment triggers) criteria
— Associated risk factors and/historical features: Recent hospitalization for ABE/COPD and documented infection with gram-negative organisms such as: Klebsiella, Pseudomonas, and other enterobacteria; patients with structural lung disease (bronchiectasis); or patients who have failed first-line macrolide therapy.
— Suspected pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, in addition to possible infection with gram-negative organisms known to cause exacerbations in patients who are risk-stratified to a more severe category (see above)

Initial (preferred agent, any class) first-line therapy: Moxifloxacin (preferred) 400 mg PO qd x 5 days; Gatifloxacin 400 mg PO qd x 7 days; Levofloxacin 500 mg PO qd x 7 days
Alternative first-line agents (fluoroquinolones): Ciprofloxacin 500 mg PO bid x 10 days (Although effective in clinical trials and recommended for acute, documented gram-negative exacerbations of COPD, ciprofloxacin is not the agent of choice when ABE/COPD is thought to be secondary to *S. pneumoniae* infection)
Alternative agents (other classes): Amoxicillin-clavulanate 875 mg PO q 12 hours x 10 days

*** Approved Indications for recommended antimicrobial agents:**
Azithromycin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*.
Clarithromycin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Haemophilus parainfluenzae*
Moxifloxacin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Haemophilus parainfluenzae*
Gatifloxacin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, Moraxella catarrhalis, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Haemophilus parainfluenzae*
Levofloxacin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Haemophilus parainfluenzae*

† OMBIRT Panel recommendations and preferences are based on a critical analysis and evaluation of published clinical trials, FDA indications, association guidelines, and pharmatectural criteria, including cost, spectrum of coverage, compliance parameters (daily dose frequency, duration of therapy, and side effects), pregnancy category, and risk of drug-drug and/or drug-disease interactions.

**** SERF** - Severity of Exacerbation and Risk Factor clinical assessment strategy.

Table 2. The SERF Risk-Stratification Pathway for Antibiotic Selection in ABE/COPD

SEVERITY OF EXACERBATION AND RISK FACTOR (SERF) SUPPORT TOOL

RATIONALE

The need for intensification and amplification of antimicrobial coverage in patients with acute exacerbations of chronic obstructive lung disease (ABE/COPD) depends on:

- Likelihood of infection with gram-negative enterobacteria
- Colonization status
- Patient's history of exacerbations and antimicrobial treatment response record
- Ability of patient to tolerate a treatment failure given his or her respiratory status
- Other factors requiring sound clinical judgment

THE SERF PATHWAY

- Based on evidence-based trials and consensus opinion
- Designed as a clinical decision support tool to help guide empiric antibiotic therapy for outpatients with ABE/COPD

Final decisions regarding drug selection should be made by the clinician on a patient-by-patient basis using a comprehensive database including history, physical examination, and other diagnostic information.

gy, efficacy, and prognostic data generated by many published clinical trials.[6,8] In general, the need for intensification and amplification of antimicrobial coverage in patients with ABE/COPD depends on the likelihood of infection with gram-negative enterobacteria, colonization status, the patient's history of exacerbations and antimicrobial treatment response record, the patient's ability to tolerate a treatment failure given his or her respiratory status, and other factors.

The SERF Pathway (*see Table 1*), which is based on evidence-based trials and consensus opinion, is designed as a clinical support tool to help guide empiric antibiotic therapy for outpatients with ABE/COPD. Final decisions regarding drug selection should be made by the clinician on a patient-by-patient basis using a comprehensive database including history, physical examination, and other diagnostic information. Specifically, the SERF pathway identifies a number of intensification of treatment trigger (IOTT) criteria that have been generated from consensus reports, reviews, and prospective trials in ABE/COPD. These factors should be considered when selecting an antibiotic for empiric outpatient treatment of ABE/COPD. The panel notes there is ample support in the medical literature for using clinical parameters identified in the SERF pathway and using IOTT criteria. (*See Tables 2 and 3.*)

Approximately one-half of all exacerbations of COPD can be attributed to bacterial infection, and antibiotic therapy has been demonstrated to improve clinical outcomes and accelerate clinical and physiologic recovery. The major pathogen continues to be *H. influenzae*, and resistance to beta-lactam antibiotics such as ampicillin can be expected in 20-40% of isolated strains.[2] Certain high-risk patients, in whom the cost of clinical treatment failure is high, can be identified by simple clinical criteria. Studies suggest, for example, that patients with significant cardiopulmonary comorbidity, frequent purulent exacerbations of COPD, advanced age, generalized debility, malnutrition, chronic corticosteroid administration, long duration of COPD, and severe underlying lung function may be more likely to fail therapy with older drugs, such as ampicillin, and that early relapse can be expected.[2]

Treatment directed toward resistant pathogens using appropriate agents may be expected to lead to improved clinical outcomes and overall lower costs, particularly if hospital admissions and respiratory failure can be prevented. Future studies examining the role of antibiotics should enroll these high-risk patients to determine if new therapies have significant clinical, quality-of-life, and economic advantages over older agents.[2]

Other authors have proposed different classification schemes. There is general agreement that ABECB can be defined as the presence of increases in cough/sputum, sputum purulence, and dyspnea. However, recent investigations suggest that the severity of ABECB also may be divided into three stages based on the history of the patient: 1) previously healthy individuals; 2) patients with chronic cough and sputum and infrequent exacerbations; and 3) persons with frequent exacerbations or more severe chronic airflow limitation.

Comparative Trials of Antibiotic Efficacy in Acute Bacterial Exacerbations of COPD

The goals of therapy for ABECB are to resolve the infection expeditiously, maintain an infection-free interval for as long as possible, and select an antibiotic with the fewest adverse effects and most favorable compliance profile. Because patients with COPD frequently are on complicated, multi-modal drug therapy (consumption of many medications with a complicated dosing schedule is not uncommon), identifying effective, compliance-enhancing regimens for ABECB is an important clinical objective. Moreover, because the key meta-analysis study supporting the efficacy of antibiotics in ABE/COPD was based on previous trials with "older" agents, it is important that practitioners are aware of more recent studies evaluating effectiveness of newer antibiotics for this condition.

One randomized, multicenter, investigator-blinded, parallel-group study compared a five-day, once-daily course of azithromycin (two 250 mg capsules on day 1, followed by one 250 mg capsule on days 2-5) with a 10-day, three-times-daily course of amoxicillin-clavulanate (one 500 mg tablet tid) in 70 patients with ABE/COPD.[8] The results of this study indicated that the administration of azithromycin once daily for five days is comparable to amoxicillin-clavulanate in the treatment of patients with ABE/COPD.[8] Because reduced frequency of dosing and shorter therapy duration may improve patient compliance, and potentially outcomes, practitioners should be aware of differences among effective agents as they relate to these compliance-sensitive parameters.

One prospective, open-label, randomized study compared the efficacy and tolerability of a 10-day course of three different

Table 3. SERF Pathway: Intensification of Treatment Trigger (IOTT) Criteria for Risk-Stratification in ABE/COPD

INTENSIFICATION OF TREATMENT TRIGGER (IOTT) CRITERIA SHOULD BE CONSIDERED WHEN SELECTING AN ANTIBIOTIC FOR EMPIRIC OUTPATIENT TREATMENT OF ABE/COPD

WHEN IOTT CRITERIA ARE PRESENT, CLINICIANS SHOULD CONSIDER AGENTS WITH EVIDENCE-BASED SUPPORT AS INDICATED AND RECOGNIZE POSSIBLE LIMITATIONS OF OLDER AGENTS SUCH AS SULFONAMIDES, PENICILLINS, AND TETRACYCLINES

IOTT criteria include the following:

- History of multiple bacterial exacerbations of COPD within a short time period (more than 3 exacerbations in < 4 months)
- Multiple antimicrobial treatment exposures
- Documentation of gram-negative (i.e., enterobacteria, pseudomonas, Klebsiella, etc.) respiratory tract colonization
- History of requiring mechanical ventilation after treatment failure of ABECB
- History of gram-negative nosocomial lower respiratory tract infection
- Chronic, systemic corticosteroid use
- Multiple emergency department visits with relapse within a 10-day period
- Supplemental home oxygen
- Smoking
- High prevalence (documented) *S. pneumoniae* resistance to penicillin
- Chronic alcoholism associated with history of gram-negative (Klebsiella) lower respiratory tract infection
- Serious co-morbidity (i.e., immunosuppression, HIV, underlying malignancy, etc.)

antimicrobial regimens commonly used to treat adults with ABECB.[10] This trial assessed clarithromycin 500 mg twice daily, levofloxacin 500 mg once daily, and cefuroxime axetil 250 mg twice daily, each administered for 10 days with food in patients with ABECB. Efficacy was determined on the basis of the clinical response to treatment and need for hospitalization and/or further antimicrobial therapy.

The investigators concluded that a high rate of clinical efficacy and tolerability was observed in this population of patients with ABECB treated with clarithromycin 500 mg twice daily, levofloxacin 500 mg once daily, or cefuroxime axetil 250 mg twice daily for 10 days.

More recently, another group, in a randomized, double-blinded, double-dummy, multicenter trial with 1:1 treatment allocation, set out to compare the safety and efficacy of oral azithromycin and levofloxacin in the treatment of outpatients with ABECB.[11] Two hundred thirty-five male or female outpatients between ages 35 and 75 who had received a clinical diagnosis of ABECB were studied. Blinded treatment arms included either oral azithromycin 500 mg on day 1 and 250 mg per day for days 2-5, or oral levofloxacin 500 mg q24h for 7 days.

Both treatments were well-tolerated, with the majority of adverse events being gastrointestinal in nature. Favorable clinical outcomes in clinically evaluable patients were demonstrated in 89% of patients receiving azithromycin and in 92% of patients receiving levofloxacin by day 4 of therapy. At day 24, the post-therapy visit, favorable responses were approximately 82% and 86%, respectively, for patients in the two treatment groups. The bacterial eradication rates of respiratory pathogens were 96% for azithromycin and 85% for levofloxacin.[11] The authors concluded that despite increasing concerns over macrolide resistance and a higher incidence of gram-negative pathogens encountered in ABECB, a five-day course of oral azithromycin was clinically and bacteriologically equivalent to a seven-day course of oral levofloxacin in the treatment of patients with ABECB.[11]

The safety and efficacy of macrolides vs. fluoroquinolones have been compared in other clinical trials, nearly all of them demonstrating, in a rather consistent manner, comparable clinical outcomes in patients with ABECB.[12,13]

A safety and efficacy study comparing moxifloxacin, an oral advanced-generation fluoroquinolone (AFQ), with azithromycin was conducted between October 1998 and April 1999. In all, 576 patients with ABECB were enrolled in 37 centers across the United States and Canada; 280 (49%) of those enrolled had ABECB (i.e., pretherapy pathogen). Patients were randomized to receive either moxifloxacin 400 mg administered once daily for five days or azithromycin for five days (500 mg qd x 1, then 250 qd x 4). For the purposes of study blinding, all patients received encapsulated tablets.[14]

The main outcome measure was clinical response at the test-of-cure visit (14-21 days post-therapy). Three patient populations were analyzed for efficacy: clinically valid, microbiologically valid (i.e., those with a pretherapy pathogen), and intent-to-treat (i.e., received at least 1 dose of the study drug). For the efficacy-valid group, clinical response at the test-of-cure was 88% for patients in each treatment group. In 237 microbiologically valid patients, corresponding clinical resolution rates were 88% for five-day moxifloxacin vs. 86% for five-day azithromycin. Bacteriological eradication rates at the end of therapy were 95% for five-day moxifloxacin and 94% for the azithromycin. Corresponding eradication rates at the test-of-cure visit were 89% and 86%, respectively. Among the 567 intent-to-treat patients (283 moxifloxacin and 284 azithromycin), drug-related events were reported for 22% and 17%, respectively. Diarrhea and nausea were the most common drug-related events reported in each group.

The investigators concluded that a five-day course of azithromycin was clinically and bacteriologically equivalent to moxifloxacin 400 mg once daily for five days for treatment of patients with ABECB of proven bacterial etiology.[14]

Short-Course Therapeutic Regimens. In a randomized, double-blind, controlled clinical trial of acute exacerbation of chronic bronchitis (AECB), azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary end point of this trial was the clinical cure rate at day 21-24. For the 304 patients analyzed in the modi-

fied intent-to-treat analysis at the day 21-24 visit, the clinical cure rate for three days of azithromycin was 85% (125/147) compared to 82% (129/157) for 10 days of clarithromycin. The following outcomes were the clinical cure rates at the day 21-24 visit for the bacteriologically evaluable patients by pathogen:

Pathogen	Azithromycin (3 Days)	Clarithromycin (10 Days)
S. pneumoniae	29/32 (91%)	21/27 (78%)
H. influenzae	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

In the safety analysis of this study, the incidence of treatment-related adverse events, primarily gastrointestinal, were comparable between treatment arms (25% with azithromycin and 29% with clarithromycin). The most common side effects were diarrhea, nausea, and abdominal pain, with comparable incidence rates for each symptom of 5-9% between the two treatment arms. In adults given 500 mg/day for three days, the discontinuation rate due to treatment-related side effects was 0.4%. Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of azithromycin were related to the gastrointestinal system, with diarrhea/loose stools (4-5%), nausea (3%), and abdominal pain (2-3%) the most frequently reported. No other treatment-related side effects occurred in patients on the multiple-dose regimens of azithromycin with a frequency greater than 1%.

Role of Infectious Precipitants in ABECB

The role of bacterial and viral-mediated infection as precipitants of acute respiratory decompensation in the setting of COPD has been controversial. Certainly, numerous studies have confirmed the role of viral infection in acute exacerbations of COPD.[15-17] In one study, 32% of patients with an acute exacerbation had evidence of viral infection.[16] In these and other investigations evaluating the role of viral infection, the most common agents identified include influenza virus, parainfluenzae, and respiratory syncytial virus (RSV).[15-19]

Interestingly, although many treatment guidelines for ABECB do not mandate empirical antimicrobial coverage of atypical organisms (e.g., *M. pneumoniae*, *C. pneumoniae*, and Legionella) for patients with ABE/COPD, studies show that atypical organisms such as mycoplasma or chlamydia occasionally may be associated with decompensation in patients with COPD. In fact, many patients with COPD have serologic evidence of previous Chlamydia infection. On the other hand, until recently, most studies suggested that acute *Chlamydia pneumoniae* infection occurs in only about 5% of acute exacerbations of COPD.[18,19] A more recent study reports *Chlamydia pneumoniae* is responsible for 4-16% of AECB in hospitalized or outpatients, although among smokers and people using steroids, the incidence is 34%.[20] The authors emphasize that *C. pneumoniae* may either be the sole causative agent or a co-agent in ABECB.

Epidemiology. The precise role of bacterial infection is more difficult to ascertain, and equally problematic to confirm in the individual patient. Nevertheless, it is clear that bacterial precipitants play an important etiologic role in ABECB.[21] In one Canadian study enrolling 1687 patients (80% of which had ABE/COPD), sputum cultures were obtained in 125 patients (7.4%). Normal flora was found in 76 of 125 sputum specimens (61%), and a pathogen was found in 49 (39%). Of all the patients having sputum cultures, *H. influenzae* was the most common pathogen, occurring in 24 cases (19%), followed by *S. pneumoniae* in 15 (12%), and *M. catarrhalis* in 10 (8%).[4] Complicating confirmation of a linkage between acute bacterial infection and clinical deterioration in COPD is the fact that patients with COPD have chronic colonization of the respiratory tree with such organisms as *S. pneumoniae*, *H. influenzae*, and *H. parainfluenzae*.[19] In addition, *M. catarrhalis* is being recognized with increasing frequency. Patients with persistent symptoms of acute tracheo-bronchitis should be suspected of having pertussis infection.

Role of Antibiotics in Improving Patient Outcomes. It should be noted that many studies were performed prior to the availability of more potent, compliance-enhancing agents, many of which, such as azithromycin and the new generation fluoroquinolones, are not only active against atypical organisms, but also against beta-lactamase-producing *H. influenzae* and *M. catarrhalis*. Furthermore, the failure rate of older antibiotics may be as high as 25%.[22,23] One approach to delineating the precise role of bacterial infection in ABECB is to evaluate the efficacy of antibiotics in producing symptomatic and functional improvement in patients during an acute exacerbation of COPD. A number of trials have been performed to assess the relationships between antibiotic treatment and resolution of symptoms, many of them using tetracycline as the therapeutic agent.[15] Some of these studies demonstrated a role for antibiotics during the acute exacerbation, while others did not find a significant advantage. However, a landmark meta-analysis of nine studies performed between 1957 and 1992 confirms that there is a small but statistically significant benefit when antibiotics are used for acute exacerbations of COPD.[3] The benefits are relatively greater for those patients with ABECB who require hospitalization.

Clinical studies of acute exacerbations of COPD are difficult to interpret because of the heterogeneous nature of COPD, diffuse symptoms that can vary spontaneously, and difficulties in defining clinical response both in the short and long terms. Although the role of bacterial infection—and as a result, empiric use of antibiotics—in COPD is somewhat controversial, the most currently available evidence shows that bacterial infection has a significant role in acute exacerbations, but its role in disease progression is less certain. Moreover, based on the preponderance of published evidence, antibiotic therapy is recommended in all patients with ABE/COPD who present with infectious symptoms (i.e., increased sputum production, change in character of the sputum, increased coughing and shortness of breath), suggesting that antimicrobial therapy will produce a better outcome.[14,24-27]

Older vs. Newer Agents. The antibiotic arsenal available for treatment of acute bacterial exacerbations of COPD includes a wide range of older and newer agents representing several drug classes. Although many of the studies confirming efficacy of antibiotics in ABE/COPD were performed with such older agents as amoxicillin and tetracycline, usage patterns are changing in

favor of newer agents such as macrolides and AFQs with a broader spectrum of coverage and compliance-enhancing features. These changes are occurring despite the increased cost of newer agents.

There is evidence-based justification for this evolution in prescribing practices.[4,24-26] In the past, antibiotics such as amoxicillin, ampicillin, tetracycline, erythromycin, and co-trimoxazole were widely employed. Many of the meta-analysis trials demonstrating the usefulness of antibiotics drew upon studies using these agents. But resistance patterns have changed.[24-29] In particular, during the last 10 years, there has been a steady rise in the frequency of beta-lactamase production by *H. influenzae* and *M. catarrhalis*, and more recently, strains of penicillin-resistant pneumococci have emerged.[25-29]

Fortunately, these older antibiotics have been joined by newer agents with either a wider spectrum of activity in vitro, better pharmacokinetics, lower incidence of side effects, more convenient dosing, and/or a shorter duration of therapy. Among the antibiotics approved for acute bacterial exacerbations of COPD, and which also have evidence-based support for their effectiveness in this condition, the azalide azithromycin, the macrolide clarithromycin, and quinolones such as moxifloxacin, gatifloxacin, and levofloxacin are playing an increasingly important role.[26-31] In addition, beta-lactamase inhibitors, including second- and third-generation cephalosporins, also are available.[25]

The MOSAIC study[32] recently was presented at the American Thoracic Society (ATS) Scientific Assembly and provides the most substantial evidence suggesting better clinical outcomes in patients treated with newer agents as compared to standard therapy with such agents as amoxicillin or cefuroxime. This trial assessed clinical and bacteriologic eradication end points—as well as reduced need for subsequent antibiotic therapy—for ABECB patients treated with the AFQ moxifloxacin when compared to standard therapy.

This multinational, double-blind, randomized study enrolled chronic bronchitis patients with a history of smoking and recurrent ABECB. An infection-free baseline was established. Patients with ABECB were randomized to five-day moxifloxacin (400 mg once-daily) or a seven-day course of what was designated as standard therapy (STD), which consisted of either amoxicillin 500 mg PO tid, clarithromycin 500 mg PO bid, or cefuroxime-axetil 250 mg PO bid. The primary end point was clinical response 7-10 days post-treatment (TOC).

The bacteriological success rates were 92% (65/71) in the moxifloxacin (MXF) treatment group and 81% (64/79) in the STD group (95% CI; 0.4, 22.1). Fewer moxifloxacin patients required post-therapy systemic antibiotics given for current ABECB in both the PP (MXF 10%, STD 15%; $p = 0.05$) and intent-to-treat (ITT) (MXF 9%, STD 15%; $p = 0.006$) groups. Rates of drug-related adverse events were comparable (MXF 7.1%, STD 4.8%). Of special importance was the observation that the time to next ABECB was 118 days for moxifloxacin compared to 132 days for the STD group ($p < 0.05$). In addition, the moxifloxacin group required fewer repeat prescriptions for ABECB. Based on these results, the investigators concluded that moxifloxacin was associated with significantly higher clinical resolution and bacteriological success rates, as well as reduced need for post-therapy antibiotics, than patients on standard therapy as defined by the study.[32]

Antibiotic Outcome-Effectiveness and Total Cost of Therapy. Unfortunately, limited data exist to guide physicians in the cost-effective treatment of ABECB. One important study, however, attempted to determine the antimicrobial efficacy of various agents and compared total outcome costs for patients with ABE/COPD.[33] For the purpose of this analysis, a retrospective review was performed of 60 outpatient medical records of individuals with a diagnosis of COPD associated with acute episodes seen in the pulmonary clinic of a teaching institution.

The participating patients had a total of 224 episodes of ABE/COPD requiring antibiotic treatment. Before review, empirical antibiotic choices were divided into first-line (amoxicillin, co-trimoxazole, tetracyclines, erythromycin); second-line (cephradine, cefuroxime, cefaclor, cefprozil); and third-line (azithromycin, amoxicillin-clavulanate, ciprofloxacin) agents. The designations "first-line," "second-line," and "third-line" were based on a consensus of resident pulmonologists, and was not intended to indicate superiority of one group of drugs vs. another. The residents were asked: "What antibiotic would you choose to treat a patient with ABE/COPD on their initial presentation, on their second presentation, and on a subsequent presentation, if each episode was separated by 2-4 weeks?"[34]

The results have potentially interesting implications for antibiotic selection in the outpatient environment. In this study, patients receiving first-line agents (amoxicillin, co-trimoxazole, tetracyclines, erythromycin) failed significantly more frequently (19% vs 7%; $p < 0.05$) than those treated with third-line agents (azithromycin, amoxicillin-clavulanate, ciprofloxacin). Moreover, patients prescribed first-line agents were hospitalized significantly more often for ABE/COPD within two weeks of outpatient treatment as compared with patients prescribed third-line agents (18.0% vs 5.3% for third-line agents; $p < 0.02$). Time between subsequent ABE/COPD episodes requiring treatment was significantly longer for patients receiving third-line agents compared with first-line and second-line agents ($p < 0.005$).[34] The high failure rate with such older agents as amoxicillin, tetracycline, and erythromycin correlates with recent reports of increasing antibiotic resistance.[34-36]

As might be expected, initial pharmacy acquisition costs were lowest with first-line agents (first-line U.S. $\$10.30 \pm 8.76$; second-line U.S. $\$24.45 \pm 25.65$; third-line U.S. $\$45.40 \pm 11.11$; $p < 0.0001$), but third-line agents showed a trend toward lower mean total costs of ABE/COPD treatment (first-line U.S. $\$942 \pm 2173$; second-line, U.S. $\$563 \pm 2296$; third-line, U.S. $\$542 \pm 1946$). The use of so-called third-line antimicrobials, azithro-mycin, amoxicillin-clavulanate, or ciprofloxacin, significantly reduced the failure rate and need for hospitalization, prolonged the time between ABE/COPD episodes, and were associated with a lower total cost of management for ABE/COPD. Well-designed, prospective studies are needed to confirm these findings and determine how critical pathways should be constructed to maximize outcome-effectiveness of antibiotics used for ABE/COPD.

Based on these results, the authors of this retrospective analysis suggest that these trends should be of interest to the following groups: 1) managed care decision-makers involved in the formulary selection process; 2) physicians whose objective is to optimize outcome-effectiveness of antibiotic therapy; and 3) patients with ABECB because definitive treatment of the initial presentation is necessary to minimize work disability, permit continuance of normal activities, reduce hospitalizations requiring more intensive therapy, and prevent further clinical deterioration from bronchitis to pneumonia.[34]

In addition, the reduction in the hospitalization rate observed with second-line and third-line agents, when compared with first-line agents, may have potential impact on the mortality of patients with COPD. In a recent study of 458 patients with COPD who required admission to hospital for ABECB, mortality was 13% after a median length of stay of 10 days. Mortality at 180 days was 35%.[37] The severity of ventilator-related impairment of lung function in patients with COPD is strongly related to death both from obstructive lung disease and from all causes.[37,38] Moreover, patients who experience frequent episodes of ABE/COPD are at risk for accelerated loss of lung function, and effective antibiotic therapy may slow this decline. The use of third-line antibiotics in the outpatient setting could decrease the number of hospitalizations and the degenerative disease process, and thus prolong the survival of patients with COPD. Further evaluation of this hypothesis is required.[34,36-39]

Based on data collected in this study, the use of azithromycin, amoxicillin-clavulanate, or ciprofloxacin for the treatment of ABECB resulted in significantly fewer physician office visits and appeared to prevent hospitalizations when compared with first- or second-line antimicrobial therapy.[34] Whether there is any difference among these agents remains to be evaluated longitudinally. Other AFQs also may provide similar advantages over older agents, and this possibility should be evaluated in prospective studies. Additionally, the repetitive nature of return visits to the ED or outpatient clinic for ABECB may assist in identifying patients who require initial treatment with more effective agents to prevent ABE/COPD-related hospital admissions and progression of the disease.

Summary of Antibiotic Therapy in ABECB

Bacterial agents appear to be particularly associated with ABECB in patients with low lung function and those with frequent episodes accompanied by purulent sputum. Non-typable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* account for up to 50% of episodes of ABECB. Gram-negative bacilli are more likely to occur in patients with more severe lung disease. Antibiotics have been used to ameliorate ABECB, to prevent ABECB, and to prevent the long-term loss of lung function that characterizes COPD. Numerous prevention trials have been conducted with fairly consistent results; antibiotics do not lessen the number of episodes of ABECB but do reduce the number of days lost from work.[40]

Most antibiotic trials have studied the impact of treatment on episodes of ABECB and results have been inconsistent, largely due to patient selection and end point definition. In patients with severe airway obstruction, especially in the presence of purulent sputum, antibiotic therapy significantly shortens the duration of symptoms and can be cost-effective. During the past 50 years, virtually all classes of antimicrobial agents have been studied in ABECB. Important considerations include penetration into respiratory secretions, spectrum of activity, and antimicrobial resistance. These factors limit the usefulness of drugs such as amoxicillin, erythromycin, and trimethoprim-sulfamethoxazole. Extended spectrum oral cephalosporins, newer macrolides, and doxycycline have demonstrated efficacy in clinical trials. Amoxicillin-clavulanate and fluoroquinolones generally should be reserved for patients with more severe disease.

While many episodes of acute exacerbation of COPD are caused by viral infection, the weight of evidence seems to indicate that patients respond to oral antibiotics—especially when the exacerbation is associated with signs and symptoms of acute bacterial bronchitis that is superimposed on COPD with a presentation characterized by fever, dyspnea, increase in sputum production, or change in the color of sputum.[41] Available antibiotics with evidence-based support for their efficacy and which have indications for ABECB have been discussed in detail.

Patients with ABECB who are deemed suitable for oral, outpatient therapy and who do not have significant IOTT criteria as outlined in the SERF pathway (*see Table 3*) and whose clinical history does not suggest the need for more extensive gram-negative coverage, should be discharged with a compliance-sensitive antibiotic that provides adequate coverage of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Macrolides/Azithromycin. Based on evidence-based trials and pharmatectural criteria (duration of therapy, reduced dosing frequency, drug interaction profile, cost, and spectrum of coverage), macrolides such as azithromycin should be considered a first-line agent in patients with ABECB who, on the basis of clinical judgment, are likely to be infected with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*.[5,7,42-49] The SCMARTI Clinical Consensus Panel acknowledged the potential advantages of a simplified dosing schedule for azithromycin consisting of 500 mg PO once daily for only three days.

When using azithromycin, a number of pharmacokinetic and drug interaction factors should be considered. Azithromycin (500 mg on day 1 and 250 mg on days 2-5) did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. However, because the effect of azithromycin on plasma levels or pharmacokinetics of theophylline is not known, until further data are available, prudent medical practice dictates careful monitoring of plasma levels of theophylline in COPD patients receiving azithromycin and theophylline concomitantly. The same precaution should be applied to patients receiving warfarin and azithromycin concomitantly. Other macrolides generally require a similar monitoring strategy.

Clarithromycin, another advanced-generation macrolide, requires a much longer course of therapy and, as a seven-day course, is more expensive ($58-$68 for a 7-day course) than a three-day course of azithromycin ($43-$46). In general, the decision to use a macrolide such as azithromycin is based on consideration of its generally acceptable cost ($43-$46 for a 3-day treat-

ment regimen), as well as its real-world advantages, which include convenient, once-daily dosing; a correct spectrum of coverage; favorable drug interaction profile; and toleration data (gastrointestinal side effects occur in about 3-5% of patients taking a 5-day, multiple-dose regimen). The oral tablet formulation permits consumption of the antibiotic without regard to food ingestion.

AFQs. Patients who are macrolide treatment failures, who are suspected of gram-negative infection with enterobacteria, and/or who present with multiple IOTT points on the SERF pathway may be effectively served by a fluoroquinolone such as moxifloxacin, levofloxacin, gatifloxacin, or ciprofloxacin, the latter of which is not recommended when *S. pneumoniae* is the presumed causative agent. Among the AFQs, because of its five-day course of therapy and because it has the lowest MICs against *S. pneumoniae*, moxifloxacin is the preferred agent.

Summary for Empiric Antibiotic Selection in Outpatients with ABECB: Risk-Directed Therapy

A variety of antibiotics are available for outpatient management of pulmonary infections. Although the selection process can be daunting, as mentioned, a sensible approach accompanied by specific recommendations for antibiotic selection in patients with outpatient bacterial infections of the respiratory tract, has been generated by the SCMARTI Clinical Consensus Panel. Regardless of the specific antimicrobial selected, one of the most important issues for the clinician is to ensure that the appropriate intensity and spectrum of coverage are provided, according to patient and community/epidemiological risk factors and patterns. The significant majority of outpatients with ABECB are appropriately managed with a macrolide. In the minority of cases (i.e., those in which infection with gram-negative organisms is suspected or if there is structural lung disease), the practitioner, based on clinical judgment, may consider shifting to and intensifying therapy with an extended spectrum quinolone.

As a rule, the clinical criteria for initiating antibiotic therapy in patients with a documented history of COPD, and who are suspected of having ABECB, include the presence of at least two of the following three symptoms: increasing purulence of sputum, increasing volume of sputum production, and increasing cough and/or dyspnea. In contrast, patients with symptoms of acute tracheobronchitis who have no history of COPD initially should not be treated with antibiotics, since antibiotics have not been shown to improve outcomes in this patient population.

Given the concerns about antibiotic overuse and the potential for emerging resistance among drug-resistant *S. pneumoniae* (DRSP) to fluoroquinolones, the SCMARTI Clinical Consensus Panel concurs with other national guidelines specifying advanced-generation macrolides such as azithromycin (or clarithromycin) as initial therapy for outpatient ABECB and use of AFQs or amoxicillin-clavulanate as alternative agents in patients who fail therapy or who have risk factors predictive of gram-negative infection. Patients who do not respond to oral therapy with one class of antibiotics (relapse) may be treated with a course of antibiotics with different gaps in coverage. Reinfections should be treated with antibiotics that have been shown to be effective in previous exacerbations.

A number of relatively inexpensive, well-tolerated antibiotics also are available, including amoxicillin, trimethoprim-sulfamethoxazole, doxycycline, and tetracycline. Antimicrobial resistance, particularly involving *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*, has become an increasing problem with many of these agents, specifically with older members of each of these drug classes. There is an increase in amoxicillin-resistant, beta-lactamase-producing *H. influenzae*. New agents are providing solutions to these difficulties. The azalide antibiotic azithromycin has the advantage of an appropriate spectrum of coverage, an acceptable safety profile, reasonable cost, and a unique three-day patient-dosing schedule that has the potential to improve patient compliance.

The newer fluoroquinolones, especially gatifloxacin and levofloxacin, are advantageous when gram-negative bacteria predominate; ciprofloxacin is another appropriate choice in this subgroup, especially for those with structural lung disease such as bronchiectasis and documented infection with gram-negative species such as Pseudomonas. When there is documented infection with DRSP, moxifloxacin is a prudent choice.

Amoxicillin clavulanate also has in vitro activity against beta-lactamase-producing *H. influenzae* and *M. catarrhalis*, as well as *S. pneumoniae*; moreover, the agent's clinical efficacy in lower RTI attributable to enzyme-producing strains has been demonstrated.

** The SCMARTI Clinical Consensus Panel & Scientific Roundtable was supported by an unrestricted educational grant from Pfizer Pharmaceuticals.*

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Statement of Financial Disclosure: In order to reveal any potential bias in this publication, and in accordance with the Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Howes is on the speaker's bureau for Roche; Dr. Stander owns stock in Pfizer; Dr. Lang, Dr. Schneider, and Dr. Smith have no financial interests related to the field of study covered by this article; for Dr. Volturo and Dr. Bosker, see the disclosure statement on page 302.

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Physician CME Questions

221. The rationale for intensification and amplification of antimicrobial coverage in patients with ABE/COPD includes which of the following?
    A. Likelihood of infection with gram-negative enterobacteria
    B. Patient's history of exacerbations and antimicrobial treatment response record
    C. Ability of the patient to tolerate a treatment failure given respiratory status
    D. All of the above

222. Studies suggest that patients are more likely to fail therapy with older drugs when which of the following factors is present?
    A. Short duration of COPD
    B. Younger age
    C. Frequent purulent exacerbations of COPD
    D. Good nutrition

223. Goals of therapy for ABECB include which of the following?
    A. Resolve the infection expeditiously.
    B. Maintain an infection-free interval as long as possible.
    C. Select an antibiotic with the fewest adverse effects and most favorable compliance profile.
    D. All of the above.

224. Investigators in a safety and efficacy study concluded that a five-day course of azithromycin was clinically and bacteriologically equivalent to moxifloxacin 400 mg once daily for five days for treatment of patients with ABECB of proven bacterial etiology.
    A. True
    B. False

225. What is the initial preferred agent of any class for first-line therapy in patients with mild ABE/COPD?
    A. Clarithromycin 500 mg PO qd x 7 days
    B. Gatifloxacin 400 mg PO qd x 7 days
    C. Azithromycin 500 mg PO qd x 3 days
    D. Doxycycline 100 mg PO bid x 7-14 days

226. Which of the following factors is included in the intensification of

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- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

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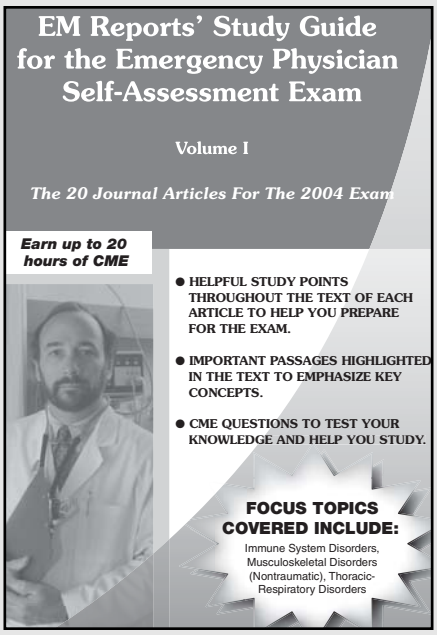

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treatment trigger criteria?

A. A single antimicrobial treatment exposure
B. History of gram-negative nosocomial lower respiratory tract infection
C. A nonsmoking patient
D. History of gram-positive respiratory tract colonization

227. Ciprofloxacin is *not* recommended when *S. pneumoniae* is presumed to be the causative agent.
A. True
B. False

228. Which of the following patients may be effectively served by a fluoroquinolone such as moxifloxacin, levofloxacin, gatifloxacin, or ciprofloxacin?
A. Patients who are macrolide treatment failures
B. Patients suspected of gram-negative infection with enterobacteria
C. Patients who present with multiple IOTT points on the SERF pathway
D. All of the above

229. Prudent medical practice dictates careful monitoring of plasma levels of theophylline in COPD patients taking azithromycin and theophylline concomitantly.
A. True
B. False

230. Short-course antibiotic treatment for ABE/COPD is always inferior to 10-day treatments.
A. True
B. False

In Future Issues:

Bronchiolitis

CME Answer Key

221. D; 222. C; 223. D; 224. A; 225. C; 226. B; 227. A; 228. D; 229. A; 230. B

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Acute Bacterial Exacerbations of Chronic Bronchitis

Outpatient Management of Bacterial Infections in the Lower Respiratory Tract (OMBIRT) Panel Treatment*† Guidelines Endorsed by SCMARTI Clinical Consensus Panel

SERF CATEGORY A**

CONDITION • SEVERITY • SUSPECTED PATHOGENS

Acute Bacterial Exacerbation of COPD (ABE/COPD)
Mild severity based on SERF (severity of exacerbation and risk factors) pathway and IOTT (intensity of treatment triggers) criteria
— Suspected pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*

Initial (preferred agent, any class) first-line therapy: Azithromycin 500 mg PO qd x 3 days
Initial (preferred AFQ): Moxifloxacin 400 mg PO qd x 5 days
Alternative first-line agents (macrolides): Clarithromycin 500 mg PO qd x 7 days
Alternative first-line agents (fluoroquinolones): Gatifloxacin 400 mg PO qd x 7 days; Levofloxacin 500 mg PO qd x 7 days
Alternative first-line agents (other classes, including generic formulations): Amoxicillin-clavulanate 875 mg PO q 12 hours x 10 days; Doxycycline 100 mg PO bid x 7-14 days; Trimethoprim-sulfamethoxazole 1 DS tablet PO bid x 7-14 days

SERF CATEGORY B

CONDITION • SEVERITY • SUSPECTED PATHOGENS

Moderate-to-severe bacterial exacerbation of COPD (ABE/COPD)
Severity based on SERF (severity of exacerbation and risk factors) pathway and IOTT (intensity of treatment triggers) criteria
— Suspected pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*

Initial (preferred agent, any class) first-line therapy: Azithromycin 500 mg PO qd x 3 days
Initial (preferred AFQ): Moxifloxacin 400 mg PO qd x 5 days
Alternative first-line agents (macrolides): Clarithromycin 500mg PO qd x 7 days
Alternative first-line agents (fluoroquinolones): Gatifloxacin 400 mg PO qd x 7 days; Levofloxacin 500 mg PO qd x 7 days
Alternative first-line agents (other classes): Amoxicillin-clavulanate 875 mg PO q 12 hours x 10 days

SERF CATEGORY C

CONDITION • SEVERITY • SUSPECTED PATHOGENS

Severe and/or frequently recurrent bacterial exacerbation of COPD (ABE/COPD)
Severity based on SERF (severity of exacerbation and risk factors) pathway and IOTT (intensity of treatment triggers) criteria
— Associated risk factors and/historical features: Recent hospitalization for ABE/COPD and documented infection with gram-negative organisms such as: Klebsiella, Pseudomonas, and other enterobacteria; patients with structural lung disease (bronchiectasis); or patients who have failed first-line macrolide therapy.
— Suspected pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, in addition to possible infection with gram-negative organisms known to cause exacerbations in patients who are risk-stratified to a more severe category (see above)

Initial (preferred agent, any class) first-line therapy: Moxifloxacin (preferred) 400 mg PO qd x 5 days; Gatifloxacin 400 mg PO qd x 7 days; Levofloxacin 500 mg PO qd x 7 days
Alternative first-line agents (fluoroquinolones): Ciprofloxacin 500 mg PO bid x 10 days (Although effective in clinical trials and recommended for acute, documented gram-negative exacerbations of COPD, ciprofloxacin is not the agent of choice when ABE/COPD is thought to be secondary to *S. pneumoniae* infection)
Alternative agents (other classes): Amoxicillin-clavulanate 875 mg PO q 12 hours x 10 days

*** Approved Indications for recommended antimicrobial agents:**
Azithromycin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*.
Clarithromycin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Haemophilus parainfluenzae*
Moxifloxacin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Haemophilus parainfluenzae*
Gatifloxacin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, Moraxella catarrhalis, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Haemophilus parainfluenzae*
Levofloxacin: Indicated for acute bacterial exacerbations of COPD caused by susceptible species of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Haemophilus parainfluenzae*

† **OMBIRT Panel** recommendations and preferences are based on a critical analysis and evaluation of published clinical trials, FDA indications, association guidelines, and pharmatectural criteria, including cost, spectrum of coverage, compliance parameters (daily dose frequency, duration of therapy, and side effects), pregnancy category, and risk of drug-drug and/or drug-disease interactions.

** **SERF** - Severity of Exacerbation and Risk Factor clinical assessment strategy.

The SERF Risk-Stratification Pathway for Antibiotic Selection in ABE/COPD

SEVERITY OF EXACERBATION AND RISK FACTOR (SERF) SUPPORT TOOL

RATIONALE

The need for intensification and amplification of antimicrobial coverage in patients with acute exacerbations of chronic obstructive lung disease (ABE/COPD) depends on:
- Likelihood of infection with gram-negative enterobacteria
- Colonization status
- Patient's history of exacerbations and antimicrobial treatment response record
- Ability of patient to tolerate a treatment failure given his or her respiratory status
- Other factors requiring sound clinical judgment

THE SERF PATHWAY

- Based on evidence-based trials and consensus opinion
- Designed as a clinical decision support tool to help guide empiric antibiotic therapy for outpatients with ABE/COPD

Final decisions regarding drug selection should be made by the clinician on a patient-by-patient basis using a comprehensive database including history, physical examination, and other diagnostic information.

SERF Pathway: Intensification of Treatment Trigger (IOTT) Criteria for Risk-Stratification in ABE/COPD

INTENSIFICATION OF TREATMENT TRIGGER (IOTT) CRITERIA SHOULD BE CONSIDERED WHEN SELECTING AN ANTIBIOTIC FOR EMPIRIC OUTPATIENT TREATMENT OF ABE/COPD

WHEN IOTT CRITERIA ARE PRESENT, CLINICIANS SHOULD CONSIDER AGENTS WITH EVIDENCE-BASED SUPPORT AS INDICATED AND RECOGNIZE POSSIBLE LIMITATIONS OF OLDER AGENTS SUCH AS SULFONAMIDES, PENICILLINS, AND TETRACYCLINES

IOTT criteria include the following:
- History of multiple bacterial exacerbations of COPD within a short time period (more than 3 exacerbations in < 4 months)
- Multiple antimicrobial treatment exposures
- Documentation of gram-negative (i.e., enterobacteria, pseudomonas, Klebsiella, etc.) respiratory tract colonization
- History of requiring mechanical ventilation after treatment failure of ABECB
- History of gram-negative nosocomial lower respiratory tract infection
- Chronic, systemic corticosteroid use
- Multiple emergency department visits with relapse within a 10-day period
- Supplemental home oxygen
- Smoking
- High prevalence (documented) *S. pneumoniae* resistance to penicillin
- Chronic alcoholism associated with history of gram-negative (Klebsiella) lower respiratory tract infection
- Serious co-morbidity (i.e., immunosuppression, HIV, underlying malignancy, etc.)

Supplement to *Emergency Medicine Reports*, November 3, 2003: "Appropriate and Outcome-Effective Antibiotic Use in Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB). The SCMARTI (Selection of Cephalosporins, Macrolides, and AFQs for Respiratory Tract Infections) Clinical Consensus Panel Report—Landmark Series in Antibiotic Management: Year 2003 Update. Part II." *Authors:* **Gregory A. Volturo, MD, FACEP,** Vice Chairman and Associate Professor, Department of Emergency Medicine, Massachusetts Medical School, Worcester; **Gideon Bosker, MD,** Assistant Clinical Professor, Section of Emergency Services, Yale University School of Medicine, Associate Clinical Professor, Oregon Health and Science University, Portland. *—On behalf of the SCMARTI Clinical Consensus Panel. Emergency Medicine Reports' "Rapid Access Guidelines."* Copyright © 2003 Thomson American Health Consultants, Atlanta, GA. **Editor-in-Chief:** Gideon Bosker, MD. **Vice President and Group Publisher:** Brenda Mooney. **Editorial Group Head:** Valerie Loner. **Specialty Editor:** Shelly Morrow Mark. For customer service, call: **1-800-688-2421.** This is an educational publication designed to present scientific information and opinion to health care professionals. It does not provide advice regarding medical diagnosis or treatment for any individual case. Not intended for use by the layman.