Managing Acute
Bronchitic Exacerbations of
Chronic Bronchitis:
Can Cost Containment and
Containing Resistance Co-exist?
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Managing Acute Bronchitic Exacerbations of Chronic Bronchitis: Can Cost Containment and Containing Resistance Co-exist?

A CME Self-Study Monograph

This special edition of the Journal of Managed Care Medicine is based on presentations and roundtable discussions that took place at the “Medical Management of COPD and the Role of Short Course Therapies” consensus meeting held in Chicago, July 17, 2004.

Audience
This program has been developed for physicians working within a managed care facility and any community physician treating acute bronchitic exacerbations of chronic bronchitis.

Needs Assessment
As concern about bacterial resistance rises, healthcare providers and managed care administrators struggle to provide treatment options across the realm of diagnoses that are effective and cost-efficient. Acute exacerbations of COPD can be singularly problematic given their potential for poor outcomes that also can result in spiraling expenses and producing still poorer life quality for the patient. Treatment guidelines provide pathways toward improved outcomes, including prevention techniques, but often go underutilized and may not adequately address the need to drive down total therapy costs.

Current tactics for managing exacerbations need to be revisited in the face of bacterial resistance patterns. New modalities can now be incorporated in regimens meant to stabilize the underlying disease state and prevent deterioration. It is vital to understand where these agents can be employed and combined with best practice patterns to quickly arrest the acute stage of bronchitis. In addition, antibiotic prescribing and dosing can be better applied to an exacerbation when there is a good understanding of antibiotic pharmacokinetics, pharmacodynamics, and the mechanisms of bacterial resistance. It is possible to utilize shorter courses of antibiotic treatment to achieve better outcomes while also limiting costs. A more in-depth understanding of the differential diagnosis of exacerbations may further lead to antibiotic avoidance altogether.

Report on Managing Acute Exacerbations of Chronic Bronchitis Consensus Panel Members

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Although the consensus panel members agreed that avoiding an exacerbation is the most cost-effective plan, appropriate drug choice and dosing during an exacerbation can be challenging. Physicians and other healthcare givers can glean helpful information from these discussions, which may prove vital to optimizing drug therapies while limiting costs in treating the acute phase of this disease.

**Learning Objectives**

After reading this supplement, physicians will be able to:

- Discuss cost-effective management of acute bronchitic exacerbations of chronic bronchitis
- Identify areas in current treatment guidelines where improvements may be made to better clinical outcomes
- Review mechanisms of bacterial antibiotic resistance and specific resistance patterns for antibiotic classes
- Strategize methods to circumvent resistant organisms through appropriate antibiotic management and the potential use of short-duration courses of antibiotics.

**Accreditation**

The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education to physicians.

**Designation Statement**

NAMCP designates this activity for a maximum of Category I credits toward the AMA Physician’s Recognition Award. Each physician should claim only those hours he/she actually spent in the activity.

To receive CME credits, read the entire monograph and answer the post-test questions. An answer sheet is available online at www.namcp.org/cmeonline.htm. Select the option for post-test and evaluation.

The release date of this activity is March 30, 2005. This activity is valid through Dec. 30, 2005. This activity is supported by an unrestricted educational grant from Pfizer Inc.

**Disclosure of Faculty Relationships and Discussion of Off-Label Uses**

Claudia G. Cote, MD, FCCP, has received grants and research support from Boehringer Ingelheim, and serves as a consultant and a member of that company’s speakers bureau.

Ronald J. DeBellis, PharmD, FCCP, has received grants and research support from Pfizer. He also serves on speakers bureaus supported by Pfizer and Boehringer Ingelheim. Information provided by Dr. DeBellis includes discussion of off-label use of pharmaceuticals.

Thomas J. Ferro, MD, has served on speakers bureaus supported by Pfizer and Boehringer Ingelheim. Information provided by Dr. Ferro includes discussion of off-label use of pharmaceuticals.

Sheila Goodnight-White, MD, has stock ownership in Pfizer and Boehringer Ingelheim, and participates in speakers bureaus supported by Novartis, Abbott, Genentech, and Aventis.

Joel B. Karlinsky, MD, MBA, participates in the speakers bureau supported by Boehringer Ingelheim.

Todd A. Lee, PharmD, PhD, has received grants and research support from Pfizer, AstraZeneca, and Boehringer Ingelheim.

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Sanjay Sethi, MD, has received grants and research support from Boehringer Ingelheim, Bayer, GlaxoSmithKline, and Pfizer. He also serves as a consultant to Aventis, Abbott, Bayer, GlaxoSmithKline, and Pfizer. He has served on speakers bureaus supported by Boehringer Ingelheim, Bayer, GlaxoSmithKline, and Pfizer. Information provided by Dr. Sethi includes discussion of off-label use of pharmaceuticals.

Donald P. Tashkin, MD, has received grant and research support from Boehringer Ingelheim and GlaxoSmithKline. He has served as a consultant to Boehringer Ingelheim, and has participated in speakers bureaus supported by Boehringer Ingelheim and Pfizer.

**Consensus Report on Managing Acute Exacerbations of Chronic Bronchitis**

Douglas B. Schwartz, MD

A panel of pulmonary and pharmacologic specialists convened in Chicago in July 2004 to discuss the current controversies and difficulties in diagnosing and treating acute exacerbations of chronic bronchitis and develop a consensus opinion to guide the management of this common malady. Because respiratory infections are so prevalent, this review provides information useful to all clinicians who provide primary care, including surgical subspecialists who function as primary clinicians.

The lack of standard terminology to describe this disease state illustrates the misconceptions in differentiating the many events affecting the course of chronic obstructive pulmonary disease. Although the term “Acute Exacerbation of Chronic Bronchitis” (AECB) is used to indicate the multifactorial deterioration of a specific condition, AECB often is attributed to bacterial infection. Similarly, although “Acute Exacerbations of Chronic Obstructive Pulmonary Disease” (AECOPD) imparts a more global list of underlying problems, these can be overlooked when treatment is directed only at an infectious mediator. “Acute Bronchitic Exacerbations of Chronic Bronchitis” (ABECPD) may more clearly identify this problem, even though it does not define the cause of bronchitis. The medical community has yet to agree on terminology.

Cases of AECB occur frequently. It is among the three most common diagnoses for people admitted to U.S. hospitals. Among patients discharged from the hospital for AECB, nearly half will be readmitted in the next six months. In-hospital mortality from AECB in patients suffering with severe COPD (FEV1~1.0L)
exceeds 10 percent; subsequent two-
year mortality in this population
approaches 50 percent. Most of us so
vividly remember caring for these
patients repeatedly that we referred
to them as “COPD in exasperation.”
To address this health burden, we
need to identify the cause of the
exacerbation, try to limit antibiotic
therapy to those likely to benefit and
its spectrum to minimize resistance
development, as well as utilize new
modalities to treat and prevent, or at
least postpone, subsequent exacerba-
tion (and exasperation).

Current guidelines for the treat-
ment of chronic bronchitis are helpful
but have not been validated scientifi-
cally, nor well publicized. In the clini-
cal setting, especially guidelines have
proliferated beyond the number for
which a competent clinician could be
expected to remember and are thus
underutilized in general practice. The
guidelines frequently refer to antibi-
otics non-specifically, rather than
emphasize use based on clinical crite-
ria predicting bacterial infection,
expected bacterial spectrum, antibiot-
ic pharmacokinetics, and considera-
tion of bacterial antimicrobial resis-
tance patterns. This has led to a one-
drug-fits-all approach that results in
many clinicians administering broad-
spectrum antibiotics to all patients
who experience symptom deteriora-
tion. The administration frequency
and duration, as well as the adverse
events associated with broad-spect-
rum antibiotics, lead some patients to
discontinue antibiotics before all bac-
teria are killed. The unnecessarily
broad spectrum allows the antibiotic
to exert undue resistance develop-
ment pressure on bacteria that other-
wise are not susceptible to these
effects. The result of excessive num-
bers of patients receiving excessively
large amounts of excessively broad
antibiotics may be development and
promulgation of resistant bacteria
responsible for common respiratory
infections. The goal of this panel was
to discuss how to identify those
patients most likely to benefit from
antibiotics (those at risk of developing
increasing symptoms from bacterial
infections), review established guide-
lines to increase their application, con-
template methods to prevent these
exacerbations, and examine ways to
address increasingly antibiotic-resis-
tant bacteria. Panelists believe this can
improve outcomes and decrease
antibiotic resistance.

In this supplement, the specialist
panel addresses the following man-
agement issues:
• Medical Management of
Acute Bronchitic Exacerbations of
Chronic Bronchitis. The authors,
Sanjay Sethi, MD, and I, review the
data associating bacterial change to
inflammatory mediators and subse-
quent disease, and use this informa-
tion to define those patients likely to
benefit from antimicrobial therapy.
They also describe the role of stan-
dard short-acting and newer long-
acting bronchodilators, evidence-
based corticosteroid use, antibiotic
selection based on patient stratifica-
tion, and the role of supporting ther-
api es in managing AECB effectively.
• Review of the National
Treatment Guidelines for Acute
Exacerbations of Chronic
Bronchitis. Thomas Ferro, MD,
introduces the features necessary to
identify chronic bronchitis, an
important exercise because all data
discussed are derived from and
therefore applicable to the popula-
tion with chronic bronchitis.
Furthermore, acute simple bronchi-
tis (bronchitis in patients without
chronic bronchitis) usually is not
associated with bacteria. The author
reviews the pathologic mechanisms
responsible for recurrent acute bron-
chitic exacerbations of chronic
bronchitis and describes the vicious-
cycle hypothesis for recurrent exac-
erbations. He delineates the role of
bronchodilators, antibiotics and anti-
-inflammatory corticosteroids in
interrupting the cycle, and describes
interventions that decrease recurrent
exacerbations development.
• Antimicrobial Mechanisms of
Resistance. Ronald DeBellis,
PharmD, FCCP, describes the mech-
anisms of antibiotic resistance, with
special attention to resistance devel-
oping in bacteria commonly infect-
ing the respiratory tract. In addition
to providing historical perspective on
antimicrobial resistance develop-
ment, he describes mechanisms asso-
ciated with resistance to penicillins,
macrolides, and quinolones. Most
importantly, translation of this infor-
mation to the office and bedside
requires examination of the effects of
laboratory-defined resistance on
clinical outcomes. The author also
offers some clues on how to over-
come microbial antibiotic resistance.
• Short-Course Antibiotic
Treatment in Respiratory Tract
Infections (RTIs). This novel
approach incorporates pharmacoki-
etic and pharmacodynamic con-
cerns to provide clinical efficacy with
short-duration antibiotic therapy.
Short-course therapy has been effec-
tive for other infections and decreas-
es concerns for drug adherence by
decreasing drug exposure duration
and adverse effects. In some condi-
tions, short-course therapy has been
associated with decreased antibiotic
resistance. Dr. DeBellis and I and
review the data available describing
efficacious short-course therapy of
sinusitis, bronchitis, exacerbations of
chronic bronchitis, and community-
acquired pneumonia. This treatment
approach offers opportunity for
direct-observed therapy, an approach
previously shown to decrease antibi-
otic resistance while improving
adherence and efficacy in patients
with HIV/AIDS and pulmonary
tuberculosis.

The panel believes these articles
will provide insight and guidelines
for practical management improve-
ment in these sometimes exasperat-
ing clinical situations.

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WORSENING OF CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is often not further defined by practitioners before treatment is applied. It is important to recognize that worsening COPD is a multifactorial entity that can result from infection, inflammation alone, or physiologic changes. Symptoms of worsening COPD are not all acute exacerbations of chronic bronchitis. Practitioners need a more systematic thought process rather than simple empiric therapy. Unfortunately, there are no physiologic markers to help narrow the diagnosis. Thus, this manuscript will narrow its discussion to the more specific entity of acute bronchitic exacerbations of chronic bronchitis (ABECB).

Once a bronchitic component is identified, various national guidelines do exist to ensure proper treatment, but these are not often implemented in practice. Guidelines, too, are subject to scrutiny as they often apply generic recommendations for antibiotics and do not take into consideration that different classes of antibiotic treat different infections and offer differing pharmacokinetics. Yet, the significant morbidity and mortality associated with this disease dictates that more attention be paid to proper treatment to improve clinical and quality-of-life outcomes. Patients hospitalized for ABECB show a mortality rate of anywhere from six to 12 percent. Mortality increases to 24 percent if the patient requires admis-
sion to the intensive care unit. Twenty-two to 32 percent of patients seen in the emergency room for the same diagnosis will suffer a relapse, requiring a return visit. Outpatient clinic management shows a similar failure rate, at 13 to 33 percent. Treatment failures may, in some part, reflect inadequate diagnosis and management.

**Diagnosis**

COPD is defined by the obstruction of airflow and can include the presence of chronic bronchitis, emphysema, and other physiologic changes. When a patient presents with one or more of the three cardinal signs of increased dyspnea, increased sputum volume, and increased sputum purulence, the diagnosis of acute bronchitic exacerbation of chronic bronchitis (ABECB) should be suspected. Exhibit 1 provides an illustration of this concept.

An acute exacerbation is characterized by an increase in these symptoms greater than the day-to-day variation, and is observed by the patient for at least 24 hours and usually up to two weeks prior to a physician visit. Symptoms are present an average of five to seven days before patients elect to be seen by a medical professional, and there is evidence that many cases which self-resolve go unreported by patients. Other causes, such as pneumonia, congestive heart failure, and pulmonary embolism will need to be excluded prior to making the diagnosis of ABECB. Unlike an acute myocardial infarction, where troponin and creatine kinase (CK) isoenzymes are diagnostic, there are no objective tests to help pinpoint ABECB. Current biological markers of inflammation, such as cytokines and IL-6, are not available and have not been studied in the routine clinical setting.

**Treatment**

When ABECB is identified, proper treatment is essential for good outcomes, as there is significant morbidity and mortality associated with the disease. Medical therapy includes the use of various bronchodilators, oxygen supplementation when needed, appropriate antibiotics, and the addition of corticosteroids. Physicians are also now seeing an increase in the use of non-invasive ventilatory support (NIV), such as BiPAP in the treatment of ABECB. In severe cases, invasive ventilation will be required.

**Bronchodilators**

A review by Dhand, et al. reiterates some important points about therapy with metered dose inhalers. First, a metered dose inhaler produces equivalent results to a nebulizer when used correctly. An albuterol inhaler has been shown to exert maximal bronchodilation with four puffs. Best practices indicate that it is always best to use a beta-agonist in conjunction with an anticholinergic in chronic drug therapy. Also, the importance of a spacer applied to the inspiratory circuit for non-ventilated patients is greatly underscored.

Tiotropium, a new long-acting anticholinergic agent, provides a new option for the management of COPD. Although it is well documented that short-acting beta agonists used during an exacerbation complement chronic long-acting beta agonists, the potential now exists to apply the same principle to anticholinergic therapy. However, studies will be needed in the future to address this question. Dose response studies with tiotropium were done on stable COPD patients, and it is interesting to consider that ABECB may involve increased cholinergic tone, which in turn may require a higher anticholinergic dose.
Antibiotics

Exhibit 2 shows that about half of ABECB patients have associated bacteria, and therefore might be expected to benefit from an antibiotic. In the community setting, subjective clinical presentation offers no evidence of true infection but antibiotics will likely be selected based solely on symptoms and signs. Fever is not useful in establishing an infectious origin in ABECB, with the presence of elevated temperature being seen in ten to 21 percent of patients. How can we better determine whether patients will benefit from antibiotics treatment in ABECB?

In 1995, a meta-analysis by Saint, et al. demonstrated improved outcomes when antibiotics are used in well-defined exacerbations, excluding asthma. A placebo-controlled, double blind randomized trial published in 2001 included 93 patients admitted to the ICU with ABECB. No glucocorticoids were administered, and they were randomized to receive placebo or ofloxacin. Those receiving the antibiotic showed a significant improvement in the primary outcomes of mortality and the need for additional antibiotics (combined p < 0.0001). Patients receiving antibiotic treatment experienced less time in the ICU, in the hospital, and on a ventilator. Sixty percent of aspirate cultures grew bacterial pathogens.

One study examined the inflammatory markers and bacterial persistence in the sputum of ABECB patients who had improved clinically and symptomatically with antibiotic treatment. In those where bacteria was eradicated by day 10, markers of inflammation had correspondingly decreased. However, 16 patients still had bacteria present on day 10, and the inflammatory markers did not go down significantly in these patients, despite an initial decrement in the first five days of treatment. Although this was an observational study, it suggests that inflammation does not resolve until the bacteria are eradicated, making a strong case for appropriate antibiotic therapy. Perhaps a future endpoint to management of exacerbations could

Exhibit 2: Etiology of ABECB

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percentage</th>
</tr>
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<tr>
<td>M. catarrhalis</td>
<td>12%</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>12%</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>22%</td>
</tr>
<tr>
<td>H. parainfluenza</td>
<td>4%</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>4%</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>4%</td>
</tr>
<tr>
<td>Gram (-)</td>
<td>4%</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>15%</td>
</tr>
</tbody>
</table>

Exhibit 3: Exacerbation Classification by Presence of Cardinal Symptoms

Cardinal symptoms:
- Increased dyspnea
- Increased sputum production
- Increased sputum purulence

Classification:
- Type 1: All three cardinal symptoms present
- Type 2: Two of three cardinal symptoms present
- Type 3: One of three cardinal symptoms present, plus fever, cough, wheeze, or a 20 percent increase in heart rate or respiratory rate
include bacterial eradication aside from clinical improvement with the development of a measurement tool for airway inflammation.

In many respiratory tract infections, the possibility of viral etiology often precludes any antibiotic treatment at all. This approach may result in suboptimal outcomes in ABECB as observed in the above-mentioned studies. Many of the published guidelines take the more traditional approach in applying the conventional, or “older” agents without regard to known resistance patterns. Their “step” methods begin with a narrow-spectrum and lowest-cost antibiotic, then move on to more broad-spectrum antibiotics for those failing initial treatment. Another school of thought is an aggressive approach that immediately employs the latest broad-spectrum antibiotic on the market in all patients. The assumption is that this drug is the best available agent, but it can be a financially prohibitive technique as well as one that fosters resistant colonization.

Another consideration currently being advocated in community-acquired pneumonia, sinusitis and otitis media is to stratify patients into subsets based on severity of illness, anticipated bacterial etiology with known resistance patterns, and expected outcomes given the existence of co-morbid conditions. But what methods should be employed to determine the difference between a severe and minor exacerbation? Patients with more severe airflow obstruction may warrant more aggressive treatment because their limited ventilatory reserve suggests they may not tolerate treatment failure without requiring hospitalization and the attendant morbidity and mortality.

Stratification techniques discussed below, extrapolated from sinusitis literature, link antibiotic choice to severity of the acute illness. Within this framework a mild infection would receive no antibiotic or one with a narrow spectrum, while severe infection would demand aggressive antibiotic therapy. A severe infection would demand aggressive antibiotic therapy. It would be expected that the severity underlying conditions such as COPD or CHF would increase the risk of an unfavorable outcome and, therefore increase the rank accordingly. Considerations should be given to host response: Is the patient malnourished and unable to produce an adequate immune response? Recent exposure to an institutional setting (e.g., daycare, hospital, etc.) as well as antibiotic use in the prior three months may also drive antibiotic selection, given the increased likelihood of exposure to gram-negative bacilli and multi-drug-resistant streptococci. Different from the traditional step-care approaches, in which a patient must fail a first-line drug before receiving a second-line agent, this approach considers that the most expensive therapy is the one that failed. Recent studies used in creating the ACCP/ACP/ASIM national guidelines indicate that older antibiotics are no less effective than newer ones, but these studies did not stratify patients to account for those who may have a true need for broad-spectrum antibiotics as initial treatment.14 Also, as with the GOLD guidelines, recommendations to incorporate local susceptibility patterns into the antibiotic equation fail to recognize that few physicians have this information available when it is needed.

The best placebo-controlled study done in the United States from Anthonisen et al. prospectively defined three categories of ABECB based on three cardinal symptoms: increased dyspnea, increased sputum production, and increased sputum purulence. Three hundred and sixty-two episodes of exacerbation in 173 patients were randomized to receive placebo, or one of three “older” antibiotics, amoxicillin, cotrimoxazole, or doxycycline. The subtypes of exacerbation are shown in Exhibit 3. In all exacerbations, 68 percent improved when treated with antibiotics, although 55 percent achieved resolution on placebo alone after reaching the three-week endpoint (p < 0.01). Yet, it should be noted that 32 percent did not improve on antibiotics, a possible indicator that the choice of antibiotics was a weakness in the study. Additionally, those receiving placebo required either additional treatment and/or hospitalization significantly more often when compared with the antibiotic group (p < 0.05). A trend was identified whereby the greatest benefit from antibiotics was experienced by the sickest patients, with the benefit declining as severity lessened (see Exhibits 4 and 5), though statistical analysis on the three subtypes was not done individually.

Co-morbid conditions were not considered in the stratification seen with Anthonisen’s study, but another study published in 2001 shows stratification of patients by co-morbidity and severity of underlying disease by multivariate regression analysis. A total of 2,414 outpatients seen in general practice for ABECB were followed. Five hundred and seven patients suffered a relapse (21 percent), requiring hospitalization (3.5 percent), an emergency room visit (7 percent), or a return to their physician (11 percent) within one month. Of those suffering relapse, increased dyspnea, coexistent ischemic heart disease, and the number of visits in the year prior, predicted an increased risk of treatment failure. In other studies, age greater than 65 years and severe chronic disease (FEV1 < 50 percent) also have been shown to be risk factors for poor outcome.16 It is then proposed that chronic bronchitis patients with exacerbation be stratified to one of two subgroups: 1) Simple Chronic Bronchitis, where none of the above risk factors are present, or 2)
Complicated Chronic Bronchitis, where one or more risk factors are present.

Canadian guidelines are being proposed based on this stratification scheme (see Exhibit 6). Currently there are no data supporting the superiority of fluoroquinolones and amoxicillin/clavulanate over other antibiotics in the complicated patients. The rationale of antibiotic choice is not clearly evidence-based, but likely the general interpretation is that simple exacerbations don’t require the most broad-spectrum (and often most expensive antibiotic). Conversely, ABECB in the complicated group is more likely to be associated with gram-negative bacilli, and these patients’ limited ventilatory reserve allows little room for error. Therefore, an effective broad-spectrum antibiotic will be prescribed regardless of cost. Amoxicillin/clavulanate offers good coverage of *H. influenzae, M. catarrhalis*, and pneumococcus and presents a good alternative in a patient with a fluoroquinolone allergy or prior fluoroquinolone treatment. The third tier has significant questions since chronic bronchial sepsis is not defined, and it is more appropriate and easy to obtain sputum for *P. aeruginosa* culture.
Corticosteroids

Now routinely accepted as an indicated treatment in hospitalized ABECB patients, debate about proper dose, need for taper, and therapy duration persists. The multi-site SCCOPE trial, done in the Veterans Health Administration medical centers, illustrates failure rates after two different corticosteroids dosing regimens compared with placebo. The results show that treatment failure emerges early with placebo, while remaining statistically improved in both a two-week and six-week steroid regimen, and divergence stays throughout six months. The two-week and six-week groups, however, were not significantly different, illustrating that long-term systemic steroids offer no additional benefit. Failure was defined most commonly as the need for additional medication use, or the need for any kind of additional interventions. This study used methylprednisolone 125mg every six hours for three days, followed by a prednisone taper. It is now a more common practice to use lower doses of methylprednisolone. Also, evidence here that steroids produce the greatest effect in the acute phase has led to a shorter course of therapy without the need for tapering.

Davies, et al. provides another placebo controlled study in severely ill, hospitalized patients. Prednisone 40 mg daily produced a significant improvement in FEV1 compared to placebo, and the length of stay was significantly shorter at seven days compared to nine days on placebo (p = 0.027).

This finding presents a good argument for lower-dose therapy with glucocorticoids. Patients are often seen as outpatients or in the emergency room and treated mostly at home. A follow-up study in patients seen in the emergency room and randomized to prednisone 40mg daily for ten days without taper, or placebo was done by Aaron, et al. Antibiotics were given to all patients. There was a 46 percent relapse rate with placebo, and a significant difference in time to relapse, but the difference in hospitalization was not significant. The somewhat high relapse rate of those receiving steroids and antibiotics, 27 percent, could relate to the choice of antibiotics (doxycycline or cotrimoxazole). The common use of steroids needs to be balanced with the known risks that includes hyperglycemia, steroid psychosis, hypertension and glaucoma. Immunosuppression carries infectious risk too. Autopsy of 222 deaths in an intensive care unit identified six patients who had invasive, disseminated aspergillosis; five of these were patients who had been on steroids for COPD.

Supportive treatment (O2, BiPAP, CPAP)

The British Thoracic Society considers non-invasive ventilation the gold standard in treatment of ABECB. Non-invasive ventilatory support benefits patients hospitalized for ABECB; it is associated with shorter stays in the intensive care unit, and decreases in intubation requirement, nosocomial infection rates, and mortality. Its use in an acute

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**Exhibit 6: Proposed Canadian Guidelines By Stratification**

<table>
<thead>
<tr>
<th>Simple, uncomplicated ABECB</th>
<th>Complicated ABECB</th>
<th>Complicated ABECB at risk for <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any age</td>
<td>• &gt; 64 years</td>
<td>• Patients with chronic bronchial sepsis</td>
</tr>
<tr>
<td>• ≤ 4 exacerbations/yr.</td>
<td>• &gt; 4 exacerbations/yr.</td>
<td>• Need for chronic corticosteroid therapy and frequent (&gt; 4/yr.) courses of antibiotics</td>
</tr>
<tr>
<td>• No co-morbid illness</td>
<td>• Serious co-morbid illness</td>
<td>• FEV &lt; 35%</td>
</tr>
<tr>
<td>• FEV1 &gt; 50%</td>
<td>• &gt; FEV1 &lt; 50%</td>
<td>• Newer fluoroquinolones or amoxicillin/clavulanate</td>
</tr>
<tr>
<td>New macrolide, new cephalosporin, or doxycycline</td>
<td>Fluoroquinolone with antipseudomonal activity</td>
<td></td>
</tr>
</tbody>
</table>

FEV1 = Forced expiratory volume in 1 second.
exacerbation should be monitored closely. Not all patients will be candidates for this form of therapy, including those having cardiopulmonary arrest, severely altered mental status, hemodynamic compromise, multi-organ failure, excessive secretions, vomiting, mechanical bowel obstruction, or an undrained pneumothorax. Nevertheless, this is a significant improvement over invasive practices and can be considered front-line treatment.\textsuperscript{21,22,23,24}

**Prevention**

**Antibiotics as preventive agents**

Long-acting beta agonist and steroid inhalers, as well as vaccinations, are well established in the prevention of acute exacerbations of COPD. Recent studies show that the newer fluoroquinolones moxifloxacin and gemifloxacin are associated with a more prolonged exacerbation-free time period when compared to antibiotics like amoxicillin, clarithromycin, or cefuroxime.\textsuperscript{25,26} Further investigation is needed before strong recommendations can be made; few direct comparisons of treatment regimens used in the United States have been made. Most recently, studies of a long-acting anticholinergic dry powder inhaler, tiotropium, show statistically significant delays in time to first exacerbation, and decreased unscheduled COPD-related healthcare visits and hospitalization.

Other authors in this supplement will discuss in greater depth another important preventive tactic: immunization.

**Conclusion**

ABECB guidelines suggest therapeutic approaches that might retard bacterial resistance, improve compliance, and provide clinical resolution. However, guidelines are subject to scrutiny as they often advise prescribing generic antibiotics that may not consider probable pathogens, local resistance patterns, antibiotic pharmacokinetic, and pharmacodynamic properties. New therapeutic agents, such as tiotropium and the latest fluoroquinolones, follow the release of treatment standard publications but should also be considered. Studies may prove these to be valuable tools not only in immediate clinical cure but also long-term reduction in morbidity. JMCM

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**References**


Review of the National Treatment Guidelines for Acute Exacerbations of Chronic Bronchitis

Thomas J. Ferro, MD

Summary
In 1996, Connors, et al. set the stage for developing guidelines for the treatment and prevention of acute exacerbations of chronic obstructive pulmonary disease (COPD) when they published the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT). This acute phase of COPD is usually termed Acute Bronchitic Exacerbations of Chronic Bronchitis (ABECB). When reviewing the many published guidelines, including those from the United States Department of Veteran Affairs (VA) and from Canada, one of the common themes is cost containment through avoidance of high-dollar antibiotics. It is important, however, to distinguish between the need to manage the cost of a single treatment modality, as opposed to the higher need to control the overall cost of appropriate control of the chronic disease and avoidance of relatively expensive acute situations. This presentation of the available data chronicles the benefit and cost of proper handling of COPD and ABECB, both in terms of monetary savings and long-term quality-of-life outcomes.

Key Points
- Introduce “vicious circle” hypothesis of COPD and the role of acute exacerbations in patient decline.
- Identify areas in current treatment guidelines where improvements may be made to better clinical outcomes.
- Discuss cost-effective management of acute bronchitic exacerbations of chronic bronchitis.

Many treatment guidelines aimed at managing chronic obstructive pulmonary disease (COPD) and the associated acute exacerbations attempt to contain the high cost of provided care. The Canadian and United States VA systems are somewhat analogous in their generalized exclusion of high-end antibiotics. However, the most cost-effective scenario would be to make therapy choices that are shown to avoid or reduce overall high-cost healthcare utilization. The ultimate “win-win” situation would be one in which COPD and ABECB are managed in an optimal fashion, while using fewer antibiotics and achieving superior outcomes. Preventive strategies should be employed to avoid antibiotic and exacerbation. It’s important to be mindful of the proper use of all treatment modalities, including antibiotic selection, for exacerbation to prevent recurrence and improve long-term outcomes. This discussion will review outcomes of ABECB in terms of severity, and look at strategies for “lung stabilization,” i.e., decreasing the likelihood of acute exacerbation, and appropriate antibiotic choice. It will also present the special cases of bronchiectasis and exacerbations in the absence of COPD.

Secondary Prevention of COPD
‘Vicious Circle’ Hypothesis
Exhibit 1 illustrates how ABECB begins a cycle that, when allowed to continue, spins obstructive lung disease out of control. Starting at the point in the circle marked by risk factors, such as smoking and the protease/anti-protease imbalance theory in COPD, it appears that all such factors lead to lung
epithelial injury. This in turn results in various diseases (emphysema, asthma, bronchiectasis, chronic bronchitis) labeled as airway obstructive diseases. Abnormal local immunity produces recurrent infections and/or exacerbation and promotes further epithelial injury. This hypothesis of worsening lung disease does not have proven statistical validity, but it should be taken seriously in view of choosing treatment targeting long-term outcomes.

Smoking cessation is believed to be the single most crucial preventive step to be taken. In susceptible individuals, smoking induces the protease/anti-protease imbalance. Kanner, et al. show that physician visits for acute episodes increase as FEV₁ decreases with continued smoking, but not necessarily in sustained quitters. It is possible that sustained quitters either have fewer exacerbations, or return to bronchitic exacerbations as a benign event with no long-term
consequences. But acute exacerbations in patients with COPD can have long-term consequences in those who continue to smoke.

Are there ways to alter the cycle of deterioration in recurrent ABECB? Recent publications with regard to moxifloxicin are a first attempt at cutting into the microbiologic etiology of exacerbations. Other advances in treatment include the introduction of a long-acting anticholinergic tiotropium, which may have a significant impact on long-range outcomes. How physicians manage steroids both during an exacerbation and in chronic management also may have implications in the long-term.

Outcomes in ABECB

The SUPPORT study by Connors, et al. clarifies the morbidity and costs associated with ABECB. From a financial point of view, ABECB is a high-cost disease if it progresses to hospitalization. This large, multi-center trial estimated that each of 1,016 patients incurred $7,400 median hospitalization costs on the index admission. These costs represent data from 1994, which would translate to nearly $15,000 in today's economy. The study indicates that 49.9 percent of the patients were readmitted within six months, incurring further annualized expense. The median length of stay was nine days, with two days in the intensive care unit. However, the mean length of stay was 14 days. Discrepancies in median and mean length of stay likely represent a subpopulation that has a disproportionately high utilization rate. This subpopulation was not defined by the authors, but likely represents patients with bronchiectasis, very low spirometric results, and other signs of advanced COPD.

Beyond cost, ABECB is also shown to produce a poor quality of life after discharge. In the above study, 50 percent of patients rated their quality of life as only fair or poor, with 14 percent being directly admitted to a nursing home upon discharge rating. Merely 26 percent were able to take care of themselves. As seen in Exhibit 2, survival is also at issue. An 11 percent mortality rate is seen with the initial hospitalization, and two years post-discharge saw only a survival rate of around 50 percent. This is somewhat analogous to the trends in morbidity and mortality seen in HIV patients having low CD4 counts, or lung cancer patients with contralateral positive lymph nodes. Predictors of mortality were found to include 1) patients with abnormal blood gases consistent with advanced exacerbations; 2) poor nutritional status as seen with low body mass index and low albumin; 3) poor functional status prior to index admission; 4) concomitant congestive heart failure; 5) advanced age.

Lung Stabilization

Glucocorticoids

In the 1940s, Dr. Fuller Albright’s discovery of treatment with adrenal powder led to systemic glucocorticoid use. Systemic glucocorticoids have now found great acceptance in the treatment of ABECB. But they, along with non-steroidal anti-inflammatory drugs, are among the most toxic class of drugs used today. Grouped together, they induce more adverse drug events in the general population every year than chemotherapy agents. Inhaled corticosteroids carry the promise of less toxicity than systemic preparations, but they may also be less effective.

The question centers on how much steroid is needed. The GOLD guideline makes recommendations for the treatment of ABECB using systemic glucocorticoids based on two recent studies. The prednisone dose in both cases is limited to 40mg daily for 15 days, with no taper required. In addition to possible (but not documented) benefit during the acute episode, this regimen has an impressive “lung stabilization” effect, decreasing the likelihood of a repeat episode of ABECB for up to 5.5 months. According to GOLD, inhaled glucocorticoids are limited to the stabilized condition and are not helpful in ABECB, though it is acceptable to continue them throughout the acute episode so as not to disrupt their management regimen. Furthermore, until new data are produced, inhaled corticosteroids are recommended in COPD only for patients with recurrent exacerbations and/or an FEV1 less than 50 percent of predicted.

Anticholinergics (AC)

Ipratropium has been around for many years as a first-line short-acting anticholinergic bronchodilator in COPD. But the recent introduction of tiotropium provides an important supplement and novel intervention for the reduction of ABECB episodes. Currently data from Europe and, as yet unpublished data from a large multicenter trial in the U.S. demonstrate improvement in hospitalizations and in the overall incidence of episodes of acute exacerbation when compared to either placebo or ipratropium at one year. Thus, tiotropium seems to have a potent “lung stabilization” effect. See Exhibit 3.

Immunization

The VA guidelines have addressed many of the above topics in mimicking the GOLD guidelines for glucocorticoids, smoking cessation recommendations, and anticholinergic therapy, though they have not as yet been updated with information about tiotropium. Another area of importance that the VA addresses is the pathogenesis of ABECB. Pneumococcus vaccine and influenza vaccine are well utilized for prevention.
A recent VA Cooperative Study shows that the use of both vaccines is efficacious in COPD patients, although the cohort was overwhelmingly older males. There is currently worldwide controversy about the use of pneumococcus vaccine in the general population, however there is little controversy when it comes to population treated by the VA. The concern is largely over antibody response, but this may not relate to outcomes sought in COPD treatment (e.g., reduction in pneumonia events and severity) because despite some debilitations, most COPD patients do not have significant deficiency of systemic immunity. The Centers for Disease Control guidelines indicate that the pneumococcus vaccine be given once at primary indication of a predisposing condition or at 65 years of age, then revaccinate every five to seven years. There is no clinical evidence that a booster vaccine gives any further protection, though laboratory evidence suggests a decline in titers over time in the absence of a booster.

### Appropriate Use of Antibiotics

Acute bronchitic exacerbations of chronic bronchitis

Infection is the number one etiology in ABECB. The SUPPORT Study of Connors, et al. underlines the importance of antibiotic intervention, if managed appropriately. What assessments can help determine when and how to use antibiotics? Eller, et al. indicate that there is a correlation between the severity of COPD and the likelihood of identifying gram-negative bacilli, as shown in Exhibit 4. Anthonisen, et al. and Stockley, et al. show a correlation between key clinical findings (e.g., worsened dyspnea, sputum volume, and sputum purulence) and response to antibiotics.
In addition, nearly all patients with purulent sputum achieved clinical cure with antibiotics. Stockley’s study compared purulent sputum to sputum that was mucoid in nature. Purulent sputum exhibited greater numbers of neutrophils, was most often Gram-positive, and showed greater culture growth than mucoid sputum. The drawback to this study is that only mucoid-producing patients received placebo, therefore it is uncertain whether those with purulence may have gotten better without an antibiotic. Conversely, non-purulence does not mean that there are no bacteria, but all patients with mucoid sputum resolved without the need for antibiotics. Also, in the outpatient setting patients are frequently unable to produce sputum on demand, therefore it’s important to look to the subjective, and often unreliable, observation of the patient.

As mentioned, the VA guidelines and many other national guidelines show no preference to newer antibiotics despite their superior antibacterial activity. In 1999, Destache, et al. helped answer the question of whether the initial cost of therapy is outweighed by the overall cost of failed therapy by looking at 60 patients with 224 ABECB episodes. This retrospective study shows lower failure rates with newer antibacterials (azithromycin, ciprofloxacin, and amoxicillin–clavulanate) compared to generics (amoxicillin, tetracycline, and erythromycin), which were state-of-the-art drugs used in studies done more than 15 years ago, such as in Anthonisen, et al. Destache, et al. showed a reduction in the cost of the overall treatment of ABECB despite higher acquisition costs with branded antibacterials compared to generics. In Exhibit 5, a $35 expenditure results in a $450 cost savings (note: scale is not symmetrical and costs are from 1994). Slight difference in failure rates translates into an increase in the number of hospitalizations with significant associated cost increases.

If acquisition cost is to be the main driver in choosing an antibiotic, the following factors should be considered in reformulating guidelines:

- ABECB is usually in the top-three diagnoses for hospital admissions.
- In the mid-1990s (Connors, et al. 1996) reported that median length of stay for the admissions was approximately nine days. Each admission was associated with approximately $7,400 in cost.

Evidence-based medicine should include pharmacoeconomic data and should also be evaluated for the objectiveness of the comparators. Much of the current literature showing antibiotic equivalence compares the target drug against placebo and parallel the results to that of a competitive product. Exhibit 6 provides an example of a head-to-head study evaluating azithromycin and clarithromycin. The results would implicate a greater cure rate with azithromycin than clarithromycin. However, it should be noted that the clarithromycin dose was one-half of that used in practice in the United States.

Acute simple bronchitis

An algorithm for simple acute bronchitis (i.e., patients with acute bronchitis who are otherwise well), was published by Gonzalez and Sande in 2000 and is reproduced in Exhibit 7. At first glance it can be confusing, and it would be unusual to wait as long as three weeks with symptoms before treating, though this may represent a lag time before the patient presents to the physician. The main point
Exhibit 6: Treating ABECB: Azithromycin Versus Clarithromycin

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin, 500 mg qd x 3d (n=102)</th>
<th>Clarithromycin, 250 mg bid x 7d (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>94</td>
<td>93*</td>
</tr>
<tr>
<td>Bacterial</td>
<td>88</td>
<td>75</td>
</tr>
</tbody>
</table>

% of Patients

* *p < 0.01

Exhibit 7: Algorithm for Managing Simple Acute Bronchitis

Acute Cough Illness
- < 3 weeks’ duration
- With or without phlegm

Patient Characteristics
- Elderly (age ≥ 65 years)*
- Immunosuppression
- COPD or CHF

Vital Sign Abnormalities
- Heart rate > 100 beats/minute
- Respiratory rate > 24 breaths/minute
- Body temperature > 38°C (100.5°F)

Is Influenza Likely?
- Yes
- No

Consider Chest Radiography to Rule Out Pneumonia
- Positive
- Negative

Treat Pneumonia

Physical Examination
- Abnormalities suggestive of consolidation or pleural effusion
- Yes
- No

Acute Bronchitis Treatment Options†
- Expectoration
- Increase Fluid Intake
- Humidify air
- Cough Relief
- Dextromethorphan or codeine
- Bronchodilator
- Pain Relief
- NSAID or acetaminophen
- Influenza Treatment
- Anti-influenza therapy if symptoms < 48 hours’ duration and high clinical suspicion of influenza

* Pneumonia in elderly persons, those with immunosuppression, and those with chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF) often presents atypically. A high index of suspicion is warranted when evaluating cough illness in these patients, even when vital signs and chest examination appear normal.

† Consider pertussis treatment if the patient has known exposure to pertussis. Follow local health department testing guidelines; pending results, treat with a macrolide-type agent.
derived from the algorithm is that once pneumonia has been ruled out, simple acute bronchitis is considered a viral illness (e.g., influenza, or other) and is not to be treated with antibiotics.19 The problem is that simple acute bronchitis may be a bacterial illness. Bordatella pertussis data from Cherry at UCLA suggest that bacteria may be a predominant cause of acute bronchitis in college students as early as six days into a syndrome of dry hacking cough.19 This should be kept in mind for younger military personnel and student health clinics.

A study by Hong, et al.17 points out that healthcare providers have the common perception that their patients expect to receive an antibiotic when visiting for an acute respiratory illness. But can prescribers help avoid unnecessary use of antibiotics and also avoid pressure from patients? One study demonstrates a method to convince people with uncomplicated bronchitis to accept being given no antibiotic. A control group received no instruction while a full intervention group received mailed literature prior to the cold and flu season. Formal training of the medical staff instructed them on when not to treat with antibiotics. This was followed by distribution of the same literature in the office during the cold and flu season. This comprehensive program lowered the number of prescribed antibiotics and increased patient acceptance. However, this approach did not work when any one of these steps was not followed, indicating the need for the patient to be healthy to assimilate the information.18

Conclusion

Despite various guideline recommendations that caution against newer antibiotics, maintaining control of the chronic disease state should be the focus in cost-containment strategies. Costs associated with failed antibiotic treatment in ABECB may outweigh the acquisition costs of more broad-spectrum agents, based on 1) a decrease in the deterioration rate at day 21 from 31 percent to 14 percent, resulting from the use of oral broad-spectrum antibacterials in ABECB patients with increases above baseline in dyspnea, sputum volume, and sputum purulence reported by Anthonisen, et al., and 2) the study of Destache, et al. showing, in mid-1990s dollars, an approximately $450 savings in the total cost of care per ABECB episode, despite an increase of approximately $30 in the average wholesale price of the antibacterials used compared to generic agents.13 The use of inhaled corticosteroids, smoking-cessation, inhaled anticholinergics, and immunization assist in stabilizing the lung and avoiding acute phase presentations. If unavailable, ABECB is then best treated with systemic glucocorticoids according to the GOLD guideline. Here, antibiotics are warranted and evidence shows that the newer fluoroquinolones, amoxicillin/clavulanate, and macrolides offer an improved clinical as well as cost outcome over the more traditional amoxicillin, tetracycline, and erythromycin. Despite various guideline recommendations that caution against newer antibiotics, maintaining control of the chronic disease state should be the focus in cost-containment strategies. JMCM

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References

WITH THE EVER-INCREASING morbidity and mortality of acute bronchitic exacerbations of chronic obstructive pulmonary disease, accurate application of therapy has become a central goal in the advancement of treatment guidelines. The core issue of antibiotic application remains a problem. As resistant strains of bacteria have become more pronounced, physicians need to remain vigilant in restraining the use of antibiotics when possible, and be precise in choosing the most effective product that will achieve the best kill rate.

Overall, deaths attributable to infectious disease have increased by 58 percent since 1980, and in patients over the age of 65, this represents a 25 percent increase. Mortality due to respiratory infections is up by 20 percent, and septicemia deaths have spiraled by an unprecedented 83 percent.4,5 Ironically, most of the antibiotics used today, particularly the broad-spectrum antibacterials, were introduced to the market after 1980.

History and Mechanisms of Resistance
Bacteria have evolved many formats for antibiotic resistance, including development of efflux pumps to remove the offensive chemical from the cell, genetic mutations that make the cell impervious to the action of the agent, and the production of enzymes that degrade or alter the product. Genetic mutations can be passed among bacteria through both replication and plasmid transfer, ensuring resistance throughout the colony. However, over time, resistant organisms that remain after an antibiotic onslaught will again be balanced by susceptible strains. How long this takes is not clearly defined. It would seem apparent that re-exposure of this flora to the same antibiotic within at least three months would select organisms for developing higher modes of resistance, rendering that agent useless.6

Some important facts about resistance should always be kept in mind. First, given enough antibiotic and time, resistance will appear. Resistance is progressive, moving from low to intermediate to high levels. Organisms that are resistant to one antibiotic will likely become resistant to others. Once selected, drug resistance will not disappear, although it may decline. Most importantly, when a patient uses an antibiotic, this will affect other people. In our institutionalized society, this may be the single most influential factor in promotion of resistance. One example is daycare centers, where we now see large colonization with multi-drug resistant organisms, such as S. pneumoniae.4,5
The “Farm to Fork Model” has huge implications in drug-resistance today. Antibiotics placed in animal feed to kill organisms in intestinal tracts are common, a practice which places a strain on the environment when it receives the excreted chemicals. In fact, agriculture accounts for 40 percent of the antibiotics sold. As a result, low levels of antibiotic are present in areas of high bacteria concentration, such as sewer systems, breeding bacteria that are now resistant to all antibiotics out into the environment. Some larger corporations are taking steps to reduce this problem by not buying meat raised with antibiotic-laced feed.

Man’s ingenuity has been unable to outpace bacterial evolution. Development of new antibiotics is slow, but society continues to use antibiotics at the same rate despite emerging resistance. Part and parcel to this is the understanding that resistance genes in bacteria predate antibiotic use by mankind, and bacteria replicate every 20 minutes.

In looking at respiratory tract infection etiology in Exhibit 1, *Haemophilus influenzae* plays a significant role, particularly in acute bronchitic exacerbations of chronic bronchitis. *H. influenzae* is a well-known human colonizer and the chief target of extended-spectrum antibiotics to overcome penicillinase production. The exhibit also illustrates the considerable presence of *Streptococcus pneumoniae* in every infection type. This is particularly alarming given the emergence of multi-drug-resistant strains around the world.

### Exhibit 1: Etiologic Agents in Community-acquired Respiratory Tract Infections

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenzae</th>
<th>Haemophilus influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute otitis media</td>
<td>30-35%</td>
<td>20-25%</td>
<td>10-15%</td>
</tr>
<tr>
<td>Acute maxillary sinusitis</td>
<td>25-30%</td>
<td>20-25%</td>
<td>8-12%</td>
</tr>
<tr>
<td>ABECB</td>
<td>7-10%</td>
<td>30-35%</td>
<td>23-25%</td>
</tr>
<tr>
<td>CAP*</td>
<td>35-55%</td>
<td>15-25%</td>
<td>2-8%</td>
</tr>
</tbody>
</table>

*Also Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila, and rarely Staphylococcus aureus.

### Exhibit 2: Evolution of Penicillin Resistance in the U.S.

- **PenR** (MIC $\geq 2.0 \mu g/mL)
- **PenI** (MIC 0.12-1.0 µg/mL)
Penicillin-resistant Pneumococcus
Penicillin-resistant pneumococcus alters the penicillin binding proteins within the cell. This is contrary to the common belief that it produces beta-lactamase. Therefore, inhibitors such as clavulanic acid and tazobactam do little against these strains and are ineffectual. The only way to overcome this mode of resistance is to change the mechanism of action, or spectrum of activity, of the chemotherapeutic agent. The evolution of resistance began with the introduction of penicillin, but steadily increased through the 1970s to reach an intermediate level of resistance. This generally could be overcome by pushing the doses of the antibiotic, but high-level resistance began to emerge after introduction of advanced-generation cephalosporins, fluoroquinolones, newer formulations of macrolides, and azolides. Ceftriaxone still maintains good activity against penicillin-resistant *S. pneumoniae*. This is believed to be due to ceftriaxone’s lack of an oral form, which precludes it from being overused in the community setting. Exhibit 2 tracks this evolution over time.11-15

Macrolide Resistance
Macrolide resistance in *S. pneumoniae* occurs primarily by two mechanisms. Plasmid-mediated methylation of 23S RNA produces high levels of resistance seen primarily in European countries, but only accounts for 25 percent of resistant strains in the U.S. More common is the activation of the efflux pump, which imparts intermediate resistance that can be overcome by increasing the dose or optimizing the mechanism of action. European use of low-dose erythromycin over long periods of time has led to high levels of resistance, with minimum inhibitory concentrations (MICs) greater than 64 mcg/ml that are not easily overcome.15

Fluoroquinolone resistance
Quinolones are useful in the treatment of ABECB, but a word of caution: they are not immune to resistance. Two mechanisms of action to resistance are known: gene mutations at the site of the mechanism of action (topoisomerase IV and DNA gyrase) or production of an efflux pump. A single gene mutation may exist after an initial exposure to a fluoroquinolone, and re-exposure within a short time frame (three months has been postulated) could lead to the second gene mutation. The key to determining if fluoroquinolone resistance will occur could be to identify patients who already have one mechanistic mutation to fluoroquinolone receptors so that a second course of treatment with a fluoroquinolone may be avoided. Because there is no test currently available, the Centers for Disease Control makes the recommendation to allow a three-to-six month wash-out period before retreatment with this antibiotic class.17

Exhibit 3 shows that as the number of fluoroquinolone prescriptions has increased, so has pneumococcal resistance at all age levels.18 Data from 1998 show that a total of 38 percent of isolates were resistant to ciprofloxacin in Hong Kong (intermediate and high combined). This can be explained by chronic use at low doses for extended durations, as
well as use in the pediatric population. Although the U.S. has not seen this high rate of resistance, there is fear that it may quickly progress to this level. In one report of four cases of levofloxacin resistance, two patients had received prior treatment with a fluoroquinolone. The MICs of isolates ranged from a low of 1.0 mcg/ml to as high as 16 mcg/ml. Three of the four resistant isolates were also resistant to moxifloxacin, and two were also resistant to gatifloxacin. Most resistance was found to be mediated by a mutation in the parC and gyrA genes rather than through an active efflux pump. This exemplifies the concept that resistance among fluoroquinolones is a class effect, in contrast to the misconception that changing the specific drugs within the class to one with a different spectrum will avoid resistance. The argument could be made that a recent exposure to any one fluoroquinolone should be a contraindication to using another one for empiric therapy.

A study of community-acquired pneumonia (CAP) illustrates prescribing habits when a patient presents to the emergency room regardless of ultimate diagnosis. Ambulatory patients (n=768) seen at six hospitals in Canada were prescribed azithromycin (36 percent), levofloxacin (32 percent) and clarithromycin (17 percent) most commonly. Univariate and multivariate analysis was done to determine the predictors for receiving levofloxacin. Age accounted for greatest odds ratio, with a 39 percent increase in prescriptions for each 10-year increase in age. This can be somewhat explained by the Canadian CAP guideline that suggests using fluoroquinolones at age greater than 65 years. Co-morbid COPD saw frequent use as well because fluoroquinolones offer good concentration in lung tissue, good bioavailability, and a spectrum covering the most likely pathogens. But if this is common practice in multiple exacerbations, this will add to resistance. The study also found that it is common to switch to a fluoroquinolone from another antibiotic, and that physicians in this setting may not see a great caseload of CAP and are more likely to give a broad-spectrum antibiotic empirically.

A University of Pennsylvania study followed two patients who received a fluoroquinolone in the emergency department at either of two hospitals and subsequently were discharged. Based on the University of Pennsylvania Antimicrobial Management Program, it was then determined whether prescribing a fluoroquinolone was appropriate. Of 100 total enrollees, 81 received a fluoroquinolone for an inappropriate indication. Fifty-three percent of these cases had another agent that was considered first-line therapy, while 33 percent had no clear evidence of infection. In the remaining 14 percent, there was an inability to assess the need for antimicrobial therapy. See Exhibit 4 for the results.

One caveat about fluoroquinolones is that they do affect the gut flora. This alone can have a tremendous influence on selecting out resistant strains that are normal colonizers at all sites.
Resistance Risk Factors

Certain patient characteristics have been identified that may predict the presence of resistant strains of *S. pneumoniae* and are referenced in Exhibit 5. Such patients then foster the spread of resistant strains by transfer to other individuals. Genes encoded for resistance are then passed to susceptible strains. Cross-resistant strains are then selected out for survival when antibiotic treatment fails to produce adequate kill. An inappropriate antibiotic dose for extended duration will co-select for resistant strains. This is further enhanced when the patient is non-adherent or when an antibiotic is not necessary, such as in the common cold.

In 1998, the CDC published the results of eight focus groups that were asked to consider the patient and physician concerns that lead to an inappropriate antibiotic prescription. In those focus groups patients were found to want a reason why they can’t get an antibiotic, and they perceived green nasal discharge as positive sign of infection. They also preferred to return to work rather than use a sick day, and interpreted an antibiotic as the answer. Physicians, in turn, felt that they wanted to help patients by giving them the antibiotic they expected. They were also encumbered by a lack of definitive diagnostic distinction between a viral and bacterial infection. Still worse, doctors in most practice settings are given a limited time to see a patient creating uncertainty when prescribing antibiotics. These factors combine to produce a scenario whereby antibiotic prescriptions are written without concern for resistance.

### Overcoming Resistance

It is possible to overcome resistance by, first and
results are seen in Exhibit 6.32. Macrolides are still clinically safe and effective. Much of the information known is in vitro data and is not necessarily transferable to in vivo applications. An example of this is the patient with no identified organisms who improves with antibiotics. Although clinical measures for this exist, physicians continue to lack microbiologic evidence. The same can be said in resistance: there are patients with resistant strains of bacterial growth, yet they respond to that antibiotic. Studies by Stahl, et al. and Gleason, et al. have shown that macrolides produce shorter hospital lengths of stay, and thus lower costs, as well as lowering mortality following treatment in the hospital.29,30 Macrolides are still clinically safe and effective. Much of the information known is in vitro data and is not necessarily transferable to in vivo applications. An example of this is the patient with no identified organisms who improves with antibiotics. Although clinical measures for this exist, physicians continue to lack microbiologic evidence. The same can be said in resistance: there are patients with resistant strains of bacterial growth, yet they respond to that antibiotic. Studies by Stahl, et al. and Gleason, et al. have shown that macrolides produce shorter hospital lengths of stay, and thus lower costs, as well as lowering mortality following treatment in the hospital.29,30

There is a lack of knowledge about the interplay between host defenses and antibiotic requirements that may vary from person to person. After all, should the expectation of antibiotics be to improve the quality of life faster in the process of saving lives? Clinicians often prolong antibiotic use while waiting for inflammatory mediators to resolve, despite bacterial kill.

But is all of this enough to consider macrolides the first-choice therapy for lower respiratory infections? An open label, prospective study in Spain compared the morbidity and mortality of patients receiving either clarithromycin or azithromycin, both with ceftriaxone. In the higher Pneumonia Outcomes Research Trial (PORT) categories 3,4, and 5,21 azithromycin produced statistically significant improvement in length of stay and mortality. The results are seen in Exhibit 6.32. Another argument in favor of macrolides comes from a 2003 paper published by Martinez, et al. One 700-bed hospital collected data on 409 patients with bacteremic pneumococcal pneumonia over 10 years. Fifty-eight percent had received a beta-lactam with a macrolide, while the remaining 42 percent received only a beta-lactam. Multivariate analysis revealed four variables independently associated with death; among them was the lack of macrolide inclusion on initial treatment (odds ratio 0.4; p = 0.03). Others included shock, age 65 years or greater, and pathogens found to be resistant to penicillin and erythromycin.31

Conclusion
Based on information available, it’s possible to arrive at some simple rules for prescribing. Of utmost importance is avoiding antibiotics for viral infections. Consider cultures and sensitivities when possible and choose the antibiotic that is guided by these results. Discontinue antibiotics in an appropriate amount of time rather than extending them for symptomatic coverage. Avoid broad-spectrum antibiotics if they are not proven necessary. As the adage “an ounce of prevention is worth a pound of cure” implies, good infection-control practices are critical. Although all resistance will not be eliminated, these measures will go a long way toward limiting the impact of resistant organisms. JMCM

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References


WHEN THE DECISION IS MADE to apply antibiotic therapy, the goal is to treat long enough to affect a clinical cure and eradicate bacteria. At the same time, treatment should be short enough to minimize side effects, improve adherence, limit potential drug interactions, and manage microbial resistance. The optimal duration of therapy for respiratory tract infections is unknown at this time, but cost effectiveness will follow when a minimum of treatment produces the desired results.

An observation by Chodosh illustrates the importance of bacterial eradication. When infection rates are tracked in patients having received either a quinolone or clarithromycin for an acute bronchitic exacerbation of chronic bronchitis (ABECB), there was no statistical difference between the two patient groups. However, there is a marginal increase in the length of time between exacerbations with quinolones, antibiotics with a broader spectrum of coverage, compared to clarithromycin. This is strictly a hypothesis-generating study showing that choosing the appropriate antibiotic can have a long-term clinical impact.

But how much of an antibiotic is needed to achieve bacterial eradication and yet minimize the risks of adverse effects and resistance? An article by Polk has outlined methods to optimize the selection and duration of antibiotic therapy. Additionally, the World Health Organization (WHO) recommends shorter, more aggressive courses of antibiotic treatment, highlighting the importance of choosing the proper antibiotic agent and optimizing the dose. By reviewing the pharmacokinetic and pharmacodynamic properties of antibiotics, it's possible to arrive at suggestions for their application to short-course methods.

Pharmacokinetic and Pharmacodynamic Considerations

Pharmacokinetics define how a drug gets to the site of action, while pharmacodynamics are the properties exhibited by the drug once it is there. Both of these characteristics can be applied to achieve a concentration at the infection site that is enough to produce a pharmacologic effect while avoiding toxicity. For example, one study looked at the epithelial lining fluid concentration of levofloxacin versus azithromycin in the lung. Levofloxacin has high concentrations initially, but as time progresses, the converse is true, while azithromycin begins to build. Azithromycin concentrates in the alveolar macrophages, which go to the

### Summary

Antibiotics are an important part of treating acute bronchitic exacerbations of chronic bronchitis (ABECB), but the medical community cannot ignore the development of bacterial resistance. In choosing to use an antibiotic, physicians must be careful to consider the true need, the proper choice of agent, and the necessary length of treatment. Although there is no current consensus on how long antibiotic therapy should be, this discussion explores the potential benefits of short-course treatment as they are currently applied to all respiratory tract infections.

### Key Points

- Relate antibiotic pharmacokinetics and pharmacodynamics to clinical applications.
- Review the impact of resistance patterns and patient compliance on antibiotic choice.
- Discuss current concepts of short-duration antibiotic courses and their potential role in the treatment of ABECB.
source of infection and create a vector for the active
drug. The duration of action is very long. A pharma-
cokinetic study with 25 healthy volunteers demon-
strates a first-phase half-life 68 hours, and a terminal
half-life of 250 hours.6

The pharmacokinetic properties of azithromycin
exhibit both time-dependent and concentration-
dependent mechanisms of action. Therefore, it is diffi-
cult to predict how the drug will work at the site of
infection. Concentration-dependent kill would
require maximizing area-under-the-curve to mini-
mum-inhibitory-concentration ratio (AUC:MIC).
Theoretically, an increase in the amount of a single
dose will affect a better kill. Blood concentration stud-
ies of azithromycin show a short, sharp rise initially,
but after four hours in all dose ranges, the drug begins
to saturate the white blood cells and is minimal in the
serum. Thus, over time, serum concentrations cannot
accurately reflect the AUC at the site of infection.7

A Medline search from 1966 to May 1998 of
azithromycin conducted by Rapp, et al. considered
relevant studies concerning microbiology, pharmacoki-
etsics, tissue concentrations, pharmacodynamics, and
the clinical effects of these parameters. The structural
modification that distinguishes azolides from
macrolides leads to optimization of pharmacokinetic
and pharmacodynamic behavior, and yields high and
sustained tissue and intracellular drug concentrations.
Drug delivery to the site of infection by phagocytes
and fibroblasts is the hallmark of azithromycin’s tissue-
directed pharmacodynamics. Metabolism is via hepatic
pathways other than cytochrome P450, thus minimiz-
ing the risk of drug interactions.8

Efficacy, safety, and tolerability of a three-day
course of azithromycin were compared to that of a
10-day course of amoxicillin/clavulanate. This study

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**Exhibit 1: PK/PD Predictors of Bacteriologic Efficacy**

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Pattern of Bacterial Killing</th>
<th>PK/PD Predictor of Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGLY, FQ</td>
<td>Concentration-Dependent</td>
<td>AUC/MIC or Cmax/MIC</td>
</tr>
<tr>
<td>Beta-Lactams</td>
<td>Time-Dependent</td>
<td>Time Above MIC</td>
</tr>
<tr>
<td>Macrolides, Azalides</td>
<td>Time-Dependent</td>
<td>AUC/MIC</td>
</tr>
</tbody>
</table>

AUC = area under serum concentration versus time curve
Cmax = peak serum concentration
MIC = minimum inhibitory concentration

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**Exhibit 2: Less Frequent Dosing Improves Adherence**

![Graph showing adherence with different dosing frequencies (qd, bid, tid, qid) with improved adherence for qid compared to qd]
was done in children with acute lower respiratory tract infections. Results show that adverse drug events occurred 35 percent of the time in the amoxicillin/clavulanate group and 10 percent of the time in the azithromycin group, but the efficacy was equivalent. The predominant adverse related event was diarrhea.  

Exhibit 1 shows that concentration-dependent antibiotics elicit the highest concentration at the site when the drug is administered, followed by the lowest trough, and will produce a better kill without perpetuating resistance. These would include aminoglycosides and fluoroquinolones. It’s possible to measure blood levels of aminoglycosides, but this isn’t standard with fluoroquinolones so one must rely on the AUC:MIC ratio to predict their kill rate. Beta-lactams are time-dependent antibiotics. The FDA states that the concentration must be above the AUC 40 to 50 percent of the time between dosing intervals in order to produce adequate kill rate. By increasing the time to 80 to 90 percent, it may be possible to shorten the duration of therapy. This concept is being promoted by WHO. Macrolides and azolides contain time- and concentration-dependent activity, AUC:MIC ratios are the best measure, as serum levels are not always reflective of true concentration.  

Concentration-dependent, bactericidal antibiotics can allow effective treatment with shorter courses. Higher peak concentrations and AUC values can provide greater pharmacodynamic coverage of pathogens with elevated MICs. Higher doses and shorter durations of therapy result in less total drug exposure to both the patient and globally, while shorter courses achieve greater patient compliance and satisfaction.

**Patient Compliance**

Compliance is a consideration in antibiotic choice because non-compliance may lead to ineffective therapy followed by deterioration of health, a potential for bacterial resistance, transmission of antibiotic resistance organisms in the community, and overall increases in the cost of therapy. To improve compliance, shorter treatment regimen and decreased dosing frequency may be coupled with decreased adverse events.

Direct comparisons of differing duration are rare, but in published compliance studies adherence has been shown to improve with shorter courses and simpler regimens. Several studies have proven that a drug dosed once daily offers significantly improved compliance rates than one that must be taken twice a day, with further deterioration in adherence as the frequency increases. In meta-analyses, compliance decreases as the dosing interval increases, as shown in Exhibit 2. It can, however, be argued that a weakness in these studies is the inclusion of acute as well as chronic illness since it has been suggested that compliance is improved regardless of interval when symptomatic disease states are considered. The impression that patients simply will not take medicines any more than twice a day is compelling nonetheless. Exhibit 3 also demonstrated the effect duration of therapy has on adherence.

Duration studies also demonstrate compelling evidence that “shorter is better.” In a study by Schrag, et al., children given five- or 10-day treatment with amoxicillin for respiratory tract infections saw an 85 percent compliance rate with the former, compared to 74 percent in the latter, a statistically significant difference (p=0.02). In this same pediatric study, those patients receiving twice the typical dose for half the usual the time showed significantly less
penicillin-resistant *Streptococcus pneumoniae* colonization in the nasopharynx (p=0.03) at 28 days, an indicator that treatment duration influences the development of resistant bacterial strains. 16

**Duration and Bacterial Resistance**

One examination of the resistance patterns of *S. pneumoniae* demonstrates that two of three risk factors for fostering resistance are a lower daily dose of a beta-lactam (OR 5.9; CI 2.1 to 16.7) and duration longer than five days (OR 3.5; CI 1.3 to 9.8).17

Note that penicillin resistance in *S. pneumoniae* can confer macrolide and quinolone resistance. Drug use in the past six months can increase drug resistance and lead to longer treatment in bacteremia in the next course. Ruhe, et al. have published results that indicate *S. pneumoniae* bacteremia due to resistant strains increases with previous exposure to anti-infectives. Further analysis also showed that a significantly higher number of patients had resistant strains when the previous treatment involved longer exposure times, as shown in Exhibit 4.18

When a patient receives antibiotics for a respiratory tract infection, bacteria in other body systems are susceptible to collateral damage. Susceptible organisms are killed, leaving resistant pathogens to colonize. A relationship has developed between the use of ceftriaxone and the manifestation of *Clostridium difficile* diarrhea.19 In another example, vancomycin-resistant enterococcus fecal density was found to be increased when patients received antibiotics that had definitive anaerobic coverage, even if the antibiotic is given for other reasons.20-22

**Short Course Antibiotic Therapy in Respiratory Tract Infections**

**Sinusitis**

Pichichero and Cohen compared a short-course of cefpodoxime, given over five days, to a standard eight-day treatment with amoxicillin/clavulanate. The cefpodoxime group was shown to have 100 percent bacterial eradication as well as clinical cure.23 Meanwhile, another group compared a three-day course of cotrimoxazole to a 10-day course and found statistically similar effectiveness in both clinical cure and bacterial eradication. It should be noted, however, that both groups only reached a less than 80 percent cure rate.24

Azithromycin 500mg daily for three days was also measured against amoxicillin/clavulanate 625mg three time daily for 10 days. The azithromycin group was found to have statistically greater clinical scores as well as aspirate-proven bacterial kill.25

**COPD Exacerbations (ABECB)**

Truncated regimens have proven useful in COPD exacerbations as well. Data on file with Pfizer while in pursuit of the Tri-Pak indication tests a typical 10-day regimen of clarithromycin 500mg twice daily against an intensive three-day course of azithromycin 500mg daily. These comparable agents exhibited equivalent clinical efficacy rates of 82 percent without any increase in side effects with the increased dose of azithromycin. Bacterial eradication proved to be thorough with the short-course azithromycin, showing a superior trend over clarithromycin in some bacteria.26

Macrolides and quinolones both produce good clinical resolution of symptoms with short-course treatment. Amsden randomized 212 patients to receive either azithromycin for five days or levofloxacin for seven days. Clinical cure rates were statistically similar in both groups.27 In another trial, five days of azithromycin compared favorably to five days of moxifloxacin, again with statistically similar clinical cure rates at five days and 26 days.28 Evidence exists that azithromycin remains in the body for an undetermined period of time, explaining equivalent efficacy with shorter courses of therapy. Gatifloxacin also was shown to be at least as effective with a five-day treatment compared to seven days, or compared to clarithromycin for 10 days.29

**Community-Acquired Pneumonia**

Current guidelines have not standardized the duration of treatment in community-acquired pneumonia (CAP). Treatment recommendations range between five and 21 days, with acknowledgment by many of the guidelines that little evidence is available to support a specific length of treatment with maximal effectiveness.26-31 One study by Halm, et al. indicates that various clinical criteria, such as pulse, respiratory rates, and temperature, stabilize after only two to four days, regardless of patient perception of cure. This possibly reflects quick bacterial kill with longer inflammatory resolution.34 One older study points out that when treated only until the patient was afebrile for 24 hours, the average therapy ranged from one to six days, resulting in 100 percent cure.35 This concept of bacterial kill versus clinical cure needs to be differentiated. In this era of resistance and lack of development of new antibiotic moieties, there may be some benefit derived from differentiating bacterial kill from clinical improvement.

Azithromycin has been effective in short-course therapies, including five-day and three-day durations. Compared with cefaclor and roxithromycin, azithromycin was found to have equivalent clinical cure rates and favorable tolerability. Proven serology in both claim greater presence of atypical organisms, where azithromycin performed well in eradication.36,37 Three days of azithromycin, 500 milligrams
orally, daily in hospitalized patients also performed well compared to clarithromycin, 250 milligrams orally, twice daily for 10 days, including those who had failed a cephalosporin course. Although results showed that azithromycin performed better in defervescence and chest X-ray clearance, it should be noted that the dose of clarithromycin was substandard in view of current usage patterns in the United States.38

Schonwald completed a study in Croatia that randomized 100 patients with atypical pneumonia with infiltrates to receive azithromycin 1.5 grams for one dose or 500 milligrams daily for three days. Both groups demonstrated equivalence in clinical cure as well as tolerability.39 This scenario could alleviate compliance problems in the future by allowing a single dose administered in the clinic setting. Future studies will be needed to confirm these results.

Evidence that hospitalized patients can receive short-course treatment exists as well, even in the intensive care unit. Using Pugin’s Clinical Pulmonary Infections Score (CPIS), see Exhibit 5,40 Singe, et al. randomized patients with scores greater than or equal to six to a standard antibiotic therapy
for 10 to 21 days, or ciprofloxacin for only three days. The short-course ciprofloxacin group experienced significantly lower rates of re-treatment and antibiotic costs, and no difference in death and ICU days was observed.43 Similarly, Chastre observed that patients with ventilator-associated pneumonia had similar outcomes with eight-day antibiotic regimens as they did with 15 days of treatment. Patients treated for only eight days showed a marked reduction in subsequent multi-drug-resistant organisms. One difficulty in the study was a higher reinfection rate with pseudomonas species, but this has little effect on clinical outcomes.42

Conclusion

By understanding the pharmacokinetics and maximizing pharmodynamic attributes of specific drugs, we can advocate short courses of appropriately administered antibiotics in RTIs and accomplish improved adherence, fewer side effects, and decreased resistance. JCMC

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References


22. Pfizer, on file.
QUESTIONS

Medical Management of Acute Bronchitic Exacerbations of Chronic Bronchitis (ABECB)

1. A patient with COPD suffering from increased breathlessness, airway obstruction, and phlegm production must always be diagnosed with an acute bronchitic exacerbation.
   a. True
   b. False

2. Acute bronchitic exacerbation of chronic bronchitis (ABECB) is a condition associated with significant morbidity and mortality, but proper diagnosis and treatment are key to improving clinical outcomes.
   a. True
   b. False

3. Three cardinal signs of acute bronchitic exacerbations include an increase in which of the following:
   a. dyspnea, dry cough, and thick sputum
   b. beta-agonist inhaler use, sputum production, and sputum purulence
   c. chest pain, dyspnea, and dry cough
   d. all of the above

4. When used correctly, a metered-dose inhaler produces clinical results equivalent to a nebulizer, particularly when a space is applied.
   a. True
   b. False

5. Which of the following is the most likely etiologic candidate in acute bronchitic exacerbations?
   a. S. pneumoniae
   b. H. influenzae
   c. atypical bacteria
   d. viruses

6. In prescribing an antibiotic for the differential diagnosis of ABECB, the patient should be:
   a. treated with a conventional antibiotic first, then retreated with a broad-spectrum antibiotic only if needed.
   b. stratified to a subgroup based on illness severity regardless of co-morbid conditions, with treatment specific to that group applied.
   c. stratified to a subgroup that is defined by both severity of illness and co-morbid condition, with treatment specific to that group applied.
   d. given the broadest-spectrum antibiotic available.

7. Which of the statements below best characterize the use of glucocorticoids in the treatment of ABECB?
   a. Antibiotics and inhaler management, including steroid inhalers, are enough to treat an acute bronchitic exacerbation, and there is no need to begin a course of systemic glucocorticoids.
   b. It is necessary to begin a glucocorticoid at a high systemic dose with a slow taper to optimize management of an acute bronchitic exacerbation.
   c. Glucocorticoids must be continued lifelong at a low dose once used in more than one exacerbation.
   d. Low-dose systemic glucocorticoids should be started immediately in an acute bronchitic exacerbation, with no need for taper, to optimize clinical outcomes when combined with antibiotic and inhaler management.

8. Non-invasive ventilation plays no role in the treatment of ABECB.
   a. True
   b. False

Review of the National Treatment Guidelines for Acute Exacerbations of Chronic Bronchitis

1. In targeting long-term outcomes and cost containment in COPD patients, which of the following factors are important to consider for managed care?
   a. smoking cessation
   b. long-acting anticholinergic use (e.g., tiotropium) immunization
   c. all of the above

2. The SUPPORT study by Connors, et al. shows that ABECB is a condition resulting in high treatment costs and poor outcomes if sub-optimally treated initially.
   a. True
   b. False

3. Systemic glucocorticoids used during an acute exacerbation and the long-acting anticholinergic tiotropium are both shown to have a “lung stabilization” effect in preventing future episodes.
   a. True
   b. False

4. Which vaccination(s) should be administered as key preventives in COPD patients?
   a. pneumococcus vaccine
   b. influenza vaccine
   c. H. influenzae vaccine
   d. a and b
   e. all of the above

5. The pneumococcus vaccine is administered at age 65, or at first risk, and then every five years with a booster every two years.
   a. True
   b. False
6. Key considerations in choosing an antibiotic treatment for ABECB should not include:
   a. hospitalization potential
   b. acquisition cost of the antibiotic
   c. cost of extended or repeat treatment risk
   d. antibacterial activity of the agent

7. Few evidence-based studies are available comparing directly competing products at equivalent doses.
   a. True
   b. False

8. Antibiotics can best be avoided in acute simple bronchitis that is viral in nature by which method?
   a. Simply deny the patient a prescription without educating him/her.
   b. Mail informative literature to patients prior to the cold and flu season with no further need for information thereafter.
   c. Mail information to patients prior to the cold and flu season, and only reinforce this with literature available in the office/clinic.
   d. Provide formal training of the medical staff, combined with mailing informative literature to patients prior to cold and flu season, and placing literature in the office/clinic.

Antimicrobial Mechanisms of Resistance

1. Resistant organisms remaining after a course of antibiotics will be minimized, if not eliminated, by susceptible organisms given enough time.
   a. True
   b. False

2. No mechanism currently exists to transfer resistance from one organism to another.
   a. True
   b. False

3. We can take measures to completely eliminate resistant organisms.
   a. True
   b. False

4. Penicillin-resistant pneumococcus is characterized by which of the following statements?
   a. It is largely through production of penicillinase and can be counteracted with beta-lactamase inhibitors.
   b. It reached high levels of resistance before such agents as advanced-generation cephalosporins, fluoroquinolones, azolides, and newer macrolides were introduced.
   c. It is an insignificant consideration in the treatment of acute bronchitic exacerbations.
   d. It occurs through the alteration of penicillin-binding proteins, necessitating a complete change in the mechanism of action in order for the chosen treatment to overcome it.

5. Macrolide resistance occurs by plasmid medication only, leading to high resistance patterns uniform across the world.
   a. True
   b. False

6. Choose the statement below that best characterizes fluoroquinolone antibiotics and resistance.
   a. Fluoroquinolones are immune to resistance as a class.
   b. Fluoroquinolones can be used in repeated bronchitic exacerbations without concern.
   c. Fluoroquinolones should have a three- to six-month wash-out period between the use of individual agents within this class.
   d. Fluoroquinolones see most resistance through the production of an efflux pump.

7. Risk factors for predicting the presence of resistant pneumococcal strains in an individual include which of the following:
   a. Age between 6 and 65 years
   b. Immunodeficiency
   c. Recent hospitalization
   d. b and c
   e. all of the above

8. With in vitro evidence that resistance to macrolides is present, it can be inferred that these antibiotics are now clinically useless.
   a. True
   b. False

Short-Course Antibiotic Treatment in Respiratory Tract Infections (RTIs)

1. Chodosh’s observational study hypothesizes that certain antibiotics may affect the exacerbation-free periods for COPD patients.
   a. True
   b. False

2. Time-dependent antibiotics, such as penicillin, would theoretically produce a greater kill with an increase in the dose.
   a. True
   b. False

3. Azithromycin, an azolide antibiotic,
   a. exhibits both time-dependent and concentration-dependent pharmacokinetics.
   b. is concentrated in the macrophages and is delivered directly to the site of infection.
   c. is metabolized by hepatic mechanisms unrelated to the CP-450 system, minimizing the interaction potential.
   d. all of the above.

4. Shorter antibiotic regimens
   a. do not have an effect on the rates of adverse drug events.
   b. can only be accomplished with antibiotics having time-dependent pharmacokinetics.
   c. improve patient compliance.
   d. are not possible due to promotion of resistance.

5. Examples of antibiotics used to treat an infection at one site while producing resistant colonization at another site include which of the following?
   a. Penicillin-resistant streptococcus colonization of the nasopharynx.
   b. Ceftriaxone use and the manifestation of C. difficile diarrhea.
   c. Increased fecal density of vancomycin-resistant enterococcus with vancomycin use.
   d. b and c
   e. all of the above

6. Treatment duration has been standardized across all guidelines and should always be continued until the patient is afebrile for 24 hours.
   a. True
   b. False