

The Role of Infection and Antibiotic Selection in Patients with Acute Exacerbation of Chronic Bronchitis

Case Study and Commentary, *Michael S. Niederman, MD*

INSTRUCTIONS



The following case study, "The Role of Infection and Antibiotic Selection in Patients with Acute Exacerbation of Chronic Bronchitis," is accompanied by a continuing medical education (CME) evaluation that consists of 5 multiple-choice questions. After reading the case study, carefully consider each of the questions in the CME evaluation on page 75. Then, circle your selected answer to each question on the CME evaluation form on page 76. In order to receive one CME credit, at least 3 of the 5 questions must be answered correctly. The estimated time for this CME activity is 1 hour.

OBJECTIVES



After participating in the CME activity, primary care physicians should be able to:

1. Know the differential diagnosis of acute exacerbation of chronic bronchitis (AECB)
2. Categorize patients with AECB on the basis of clinical features
3. Describe the bacteriology of AECB
4. Describe the rising frequency of antibiotic resistance among the common pathogens associated with AECB
5. Understand the benefits of antibiotics in AECB
6. Use patient categories as a basis for selecting antibiotic therapy

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects at least 15 million Americans, 12.5 million of which have a component of this illness characterized as chronic bronchitis [1,2]. Because the airway of the bronchitic patient has abnormal mucus composition, mucus quantity, and mucociliary clearance, patients with chronic bronchitis are commonly colonized and infected by bacteria; at least half of all acute exacerbations of chronic bronchitis (AECB) are bacterial in nature.

The treatment costs associated with this disease are significant. In a recent study [3], the cost of inpatient care for AECB was estimated at \$1.5 billion per year, reflecting the \$1.1 bil-

lion cost of treating 207,540 inpatients aged 65 years or older and the \$0.4 billion cost of treating 74,000 inpatients younger than 65. In this study, most admitted patients of any age had multiple medical comorbidities, but comorbid illness was more common in the older patient group. Older patients also had a longer length of stay (6.3 days, compared with 5.8 days for younger patients). Although the study found it difficult to measure the frequency of outpatient care for chronic bronchitis, it was estimated that at least 10 million visits were made annually (4.2 million by patients under 65), for a total outpatient cost of \$770 million. These data show that the major cost increment in this illness, as in other respiratory infections, is admission to the hospital and that the cost of outpatient care is approximately half the cost of inpatient care, even though outpatient care is provided 30 times more often.

Despite these observations, many physicians underestimate the importance of acute exacerbations, regarding them as a minor annoyance to the COPD patient. However, 20% to 60% of patients admitted to an intensive care unit (ICU) for an acute respiratory decompensation will require mechanical ventilation, with a mortality rate ranging from 10% to 30% [4]. In 1 recent study [4], the 180-day mortality rate for those older than 65 years was 47%. Although the need for mechanical ventilation did not by itself predict short- or long-term outcomes, 180-day mortality was predicted by the degree of nonrespiratory organ dysfunction and the extent of advanced respiratory system dysfunction (as reflected by respiratory rate and arterial blood gas values).

Controversy exists regarding the value of antibiotic therapy during exacerbations. Patients without chronic lung disease who get acute bronchitis are commonly infected by viruses and rarely need antibiotics, and giving antibiotics routinely may add to the problem of antibiotic abuse and antimicrobial

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resistance [5]. Among patients with chronic bronchitis, antibiotics have benefit for certain patients during exacerbation, leading to a more rapid resolution of symptoms and return of peak expiratory flow rates (PEFR) [6,7]. However, it is often difficult to differentiate chronic bronchitis patients who need antibiotics from those who do not because the same bacteria can be present as colonizers when the patient is well and as pathogens when the patient is ill. The continual presence of bacteria in the airways of chronic bronchitis patients makes it difficult to use traditional tools such as sputum culture to determine whether antibiotic therapy is needed [8,9].

Antibiotics have benefit for selected patients with AECB, but different patients need different antibiotic therapies. Recent studies have shown that antibiotics can be selected for patients with AECB by categorizing patients on the basis of risk factors for specific pathogens, the likelihood of those pathogens being drug-resistant, and according to the patient's ability to "tolerate" an exacerbation. Such profiling recognizes that the more complex patient, the patient with borderline physiologic reserve, and the patient with risk factors for resistant organisms will need a more aggressive, broad-spectrum approach to therapy than the patient with earlier forms of the disease and less severe illness.

CASE STUDY

Initial Presentation



A 75-year-old man presents to his primary care physician with a complaint of cough with thick, yellow sputum, fever to 100.3°F, and increased shortness of breath of 3 days' duration.

History

The patient states that he is coughing up more sputum than his usual amount, which he describes as 1 teaspoon of clear, white sputum on waking that he has had daily for more than 5 years. He denies chest pain or shaking chills. In addition to daily cough and sputum production, he experiences dyspnea after mild exertion, such as climbing 1 flight of steps. When he became ill 3 days ago, his dyspnea increased and has been unresponsive to inhaled ipratropium as often as 4 puffs every 4 hours. He denies orthopnea, nocturnal awakening with shortness of breath, or leg edema.

In the past year, the patient has had 4 similar episodes. All were treated with antibiotics, and 2 episodes were treated with a 10-day course of tapering doses of corticosteroids. The last episode occurred 8 weeks ago and was treated with a course of amoxicillin/clavulanate accompanied by a tapering course of corticosteroids. The patient recovered from that episode and has been well for the past 6 weeks.

The patient smoked 2 packs of cigarettes per day for 50 years but quit 10 years ago after a myocardial infarction. Past medical history also includes prostate cancer and con-

gestive heart failure. Baseline medications include digoxin 0.25 mg daily, furosemide 40 mg daily, potassium 20 mEq daily, and inhaled ipratropium 2 puffs 4 times daily.

Physical Examination

The patient has moderate dyspnea on physical examination. Respiratory rate is 26 breaths/minute; pulse, 96 bpm; temperature, 100°F; blood pressure, 125/76 mm Hg. Cardiac examination reveals a regular rhythm and a grade II/VI systolic ejection murmur with an inspiratory S₃. Lung examination reveals a hyperinflated chest, diffusely reduced air entry, expiratory prolongation, and diffuse rhonchi without focal crackles. There is trace pretibial edema, a finding not present on prior examination when the patient was stable. Jugular venous distention to 8 cm above the sternal angle at 30 degrees is noted, a finding present on prior examination. Arterial oxygen saturation (SaO₂) on room air is 93%. The remainder of the physical examination is unremarkable.

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- What are the diagnostic considerations in this patient?
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Diagnostic Considerations

Chronic bronchitis is defined as recurrent cough with sputum production for 3 months of the year in 2 consecutive years. Thus, as evidenced by the history, this patient has chronic bronchitis and has had it for at least 3 years. Patients with chronic bronchitis are prone to exacerbations, which are characterized by increased dyspnea, increased sputum volume, and increased sputum purulence [7]. Anthonisen and colleagues [7] used these 3 cardinal symptoms of exacerbation to create a schema for grading the severity of an exacerbation: patients with all 3 symptoms are considered to have a type I exacerbation, patients with 2 symptoms a type II exacerbation, and patients with only 1 symptom a type III exacerbation.

This patient appears to have an acute type I exacerbation. However, it is important to consider a broad differential diagnosis in such a patient because not all COPD patients with the cardinal symptoms of exacerbation have bacterial bronchitis (Table 1). The patient could have a viral exacerbation or an irritative bronchitis due to allergic or chemical factors. Other diagnoses to be considered are acute pneumonia, worsening of congestive heart failure, bronchospasm (including that induced by gastroesophageal reflux), pneumothorax, and pulmonary embolus.

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- What are the next steps in the evaluation of the patient presenting with suspected AECB?
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Additional Clinical Assessment

In the early evaluation of the patient with suspected AECB, the physician must assess severity of illness, determine whether hospitalization is necessary, and rule out processes other than AECB.

Severity of Illness

Severity of illness can be determined based on historical and physical examination findings. Assessment of oxygenation status is important to determine the need for supplemental oxygen. If the SaO₂ is less than 90%, the patient should be admitted to the hospital for supplemental oxygen, unless he is receiving long-term home oxygen therapy. Also, if SaO₂ is less than 90%, measurement of arterial blood gas, which includes a measurement of carbon dioxide tension, is usually necessary, particularly if hypercapnia is suspected. If there are no signs of hypercapnia or hypoxemia, as in this patient, assessment of oxygenation by oximetry is adequate.

Need for Hospitalization

There are no prognostic scoring systems that predict the need for hospitalization based on severity of exacerbation in AECB. However, such systems do exist for patients with community-acquired pneumonia (CAP); one of the most useful is the British Thoracic Society rule, which states that a patient with CAP is at increased risk of death if 2 of the following 4 features are present: respiratory rate \geq 30 breaths/minute, diastolic blood pressure \leq 60 mm Hg, BUN level $>$ 19.6 mg/dL, and confusion [10]. The rule provides a useful guideline for deciding on the site of care for CAP patients and may also be applied to AECB patients.

Investigation of Other Causes

The major diagnostic test to rule out causes of dyspnea other than AECB is the chest radiograph. If physical findings make other diagnoses unlikely, this test may not be needed. In the case patient, for example, there are no focal physical findings to suggest CAP or clinical signs of worsened congestive heart failure or pneumothorax, and the history does not suggest pulmonary embolus or allergic/chemical tracheobronchitis. Thus, the likely diagnosis is AECB. Although a chest radiograph is not necessary in this case, it should be considered in other patients with a similar history if other diagnoses cannot be ruled out.

Initial Assessment


 The physician makes the diagnosis of a moderately severe episode of AECB, as suggested by the presence of all 3 cardinal symptoms of exacerbation, an elevated respiratory rate, and a low-grade fever. The patient's underlying congestive heart failure does not appear to have worsened during the exacerbation. Per the British Thoracic

Table 1. Differential Diagnosis of Acute Exacerbation of Chronic Bronchitis

Bacterial bronchitis
Common organisms: <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Moraxella catarrhalis</i>
Less-common organisms: gram-negative bacteria, <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i>
Viral bronchitis
Community-acquired pneumonia
Allergic or chemical tracheobronchitis
Congestive heart failure
Bronchospasm, including that induced by gastroesophageal reflux
Pulmonary embolus
Pneumothorax

Society rule, his features do not suggest the need for hospitalization.

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- **Should this patient receive antibiotic therapy?**
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Need for Antibiotic Therapy

As previously mentioned, approximately half of all exacerbations, both in outpatients and inpatients, are bacterial in origin. This conclusion is based on evidence from bronchoscopy studies with quantitative cultures demonstrating that approximately half of all patients with mild or severe exacerbations have more than 10³ organisms per milliliter in a protected specimen brush sample [11,12]. Antibiotics are likely to be of limited benefit for nonbacterial exacerbations. However, it is difficult, if not impossible, to tell whether an exacerbation is bacterial in origin based on clinical features. In 1 study that defined the etiologic nature of exacerbations by bronchoscopic quantitative cultures, patients with bacterial and nonbacterial episodes had virtually identical findings with regard to fever, leukocytosis, hypoxemia, duration of symptoms, and an acute physiologic score [11].

The current recommendation is to offer therapy to any patient with at least 2 of the 3 cardinal symptoms of exacerbation. This recommendation is based on prospective randomized controlled trials that have shown that these individuals benefit from such therapy in the way of greater frequency of success, fewer failures, and a more rapid return of PEFR compared with similar patients who do not receive antibiotic therapy [6,7]. In the largest placebo-controlled trial of antibiotics for exacerbation, patients with only 1 symptom did no better with antibiotics compared with placebo [7]. The case patient has all 3 cardinal symptoms, suggesting that

he has an acute exacerbation of sufficient severity to benefit from antibiotic therapy.

Although the goal is to give antibiotics to patients who can most benefit (ie, those with bacterial exacerbations), antibiotic therapy in patients with viral exacerbations may reduce the risk of developing secondary bacterial infection [13]. In addition, antibiotics can lower the density of bacteria colonizing the airway. In doing so, they may break the cycle of illness that begins with airway colonization, which leads to inflammation by the patient and from bacterial exoproducts, which in turn leads to a loss of lung function because of the damage resulting from these inflammatory events [14,15]. If antibiotics break this cycle, they can possibly help to slow the loss of lung function common in COPD.

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- **Which organisms are most likely to cause exacerbation and what is the likelihood that these organisms are antibiotic-resistant?**
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Causative Pathogens

The organisms that most commonly cause AECB are the big three—*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. The frequency of these organisms and the likelihood that they are antibiotic-resistant depends on the patient's risk-factor profile. In outpatients with mild exacerbations, *H. influenzae* predominates, followed by pneumococcus and *M. catarrhalis*; gram-negative infection is relatively uncommon [12]. In patients with severe exacerbation, *H. influenzae* is less common, with *Haemophilus parainfluenzae* being the most common organism isolated from bronchoscopy samples; gram-negative bacteria also are frequently isolated [11]. In a study of 50 mechanically ventilated patients with severe exacerbation, potentially pathogenic microorganisms were identified in 72% of patients, including 28% who had *Pseudomonas aeruginosa* or other enteric gram-negative bacteria [16].

H. influenzae is the most common organism leading to exacerbation; the organism is usually nonencapsulated and thus cannot be typed. This gram-negative coccobacillary rod can produce a variety of exoproducts (such as pyocyanin) that injure the respiratory epithelium and initiate a host inflammatory response that may lead to a cycle of colonization, tracheobronchial injury, and a subsequent increased risk of airway infection, along with an accelerated loss of lung function. A common exoproduct is a bacterial β -lactamase enzyme that can digest and destroy traditional β -lactam antibiotics such as ampicillin or amoxicillin. It has been estimated that up to 40% of *H. influenzae* produce this enzyme and that some organisms produce enough β -lactamase to be resistant to amoxicillin/

clavulanate [17]. In 1 study, 2.5% of all of these organisms were β -lactamase-negative yet ampicillin-resistant due to the presence of altered penicillin-binding proteins [17]. Thus, antibiotic resistance is very common with this organism and is especially likely if the patient has had multiple previous courses of antibiotics, as the case patient has.

β -Lactamase production is even more common with *M. catarrhalis*, as suggested by a study that found these enzymes in 95% of 723 isolates [18]. *M. catarrhalis* is a gram-negative coccus that for many years was thought to be a harmless oral commensal. However, it has been isolated in pure culture from patients with both CAP and AECB and is now recognized as a pathogen. When this organism is considered the likely cause of an exacerbation, β -lactam resistance should be assumed to be present.

Pneumococcus is also common in AECB and is increasingly resistant to common antibiotics. Because the pneumococcal capsule plays a role in disease pathogenesis, the pneumococcal vaccine is of value for COPD patients and should be given to all COPD patients. Pneumococcal resistance may be present in as many as 40% of all isolates, but much of this resistance is intermediate rather than high-level resistance. The implications of resistance for antibiotic therapy are uncertain, since patients with CAP have the same outcome whether pneumococcus is penicillin-sensitive or resistant [19]. Resistance among pneumococci is more likely if patients have the following risk factors: age older than 65 years, alcoholism, β -lactam therapy within the past 3 months, multiple medical comorbidities, and immunosuppressive illness [20].

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- **How does a patient's clinical profile relate to the patient's risk for specific pathogens?**
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All patients are at risk for infection with the core organisms *H. influenzae*, pneumococcus, and *M. catarrhalis*. As patients become increasingly complex, the likelihood of antibiotic resistance among these organisms increases as does the frequency of gram-negative organisms, which are more difficult to treat. Further, as the patient becomes more complex, the likelihood of therapy failure with simple antibiotics increases. In a study of 471 patients with AECB, the likelihood of failing antibiotic therapy for exacerbation increased in relation to the presence of cardiopulmonary disease and the frequency of exacerbations in the previous year, with the highest rates of failure occurring in patients with chronic heart and lung disease and with more than 4 exacerbations per year [21].

Patient characteristics may be used to define subgroups of patients at risk for specific pathogens so that antibiotic

Table 2. Antibiotic Therapy Options for Acute Exacerbation of Chronic Bronchitis (AECB)

Subgroup	Patient Profile	Likely Pathogens*	Therapy Options†
Simple AECB	Any age, < 4 exacerbations per year, no comorbid illness, FEV ₁ > 50% of predicted	Core organisms, <i>H. parainfluenzae</i> ; β-lactamase resistance is possible but not common.	Macrolides (azithromycin, clarithromycin), new cephalosporins (cefepodoxime, cefuroxime, cefprozil), doxycycline
Complicated AECB	Age ≥ 65 OR > 4 exacerbations per year OR comorbid illness OR FEV ₁ ≤ 50% of predicted but ≥ 35% of predicted	Core organisms, but often drug-resistant pneumococci or β-lactamase-producing <i>H. influenzae</i> or <i>M. catarrhalis</i> ; also some risk for enteric gram-negative bacteria	Fluoroquinolones or amoxicillin/clavulanate
Complicated AECB at risk for <i>P. aeruginosa</i>	Chronic bronchial sepsis OR need for chronic corticosteroid therapy OR frequent (> 4/year) courses of antibiotics OR FEV ₁ < 35% of predicted	Core organisms PLUS drug-resistant enteric gram-negative bacteria, drug-resistant pneumococci, β-lactamase-producing <i>H. influenzae</i> and <i>M. catarrhalis</i> , <i>P. aeruginosa</i>	Quinolone with antipseudomonal activity (ciprofloxacin)

*Core organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.

†Therapy is indicated for type I and type II exacerbations.

therapy may be targeted against the offending organisms [14,22]. Based on historical information and lung function, patients may be categorized into 1 of 3 categories: (1) simple bronchitis, (2) complicated bronchitis, or (3) complicated bronchitis at risk for infection with *P. aeruginosa* (Table 2). To categorize patients, it is necessary to know the following patient information:

- Age
- Frequency of exacerbations
- Presence of comorbid cardiopulmonary disease
- Frequency of antibiotic therapy
- Use of corticosteroids
- Severity of obstructive airways disease (FEV₁ as percentage of predicted normal)

Also to be considered is the presence of chronic bronchial sepsis, or chronic purulent sputum production on a daily basis, a finding correlated with the presence of *P. aeruginosa* and possibly bronchiectasis [15].

As reflected by its inclusion in the bulleted list above, the severity of obstructive airways disease impacts antibiotic selection. In 1 study, as lung function became progressively worse, the bacteria that most often were the cause of an exacerbation shifted from pneumococcus to *H. influenzae* and *M. catarrhalis* to *P. aeruginosa* and gram-negative organisms, which were most common in patients with the most severe impairment in lung function [23]. Although lung function tests should be measured at baseline, during treatment of an exacerbation the PEFR can be measured daily to assess response to therapy.

• What factors should be considered in selecting an antibiotic?

Antibiotics should be selected according to patient subgroup, as presented in Table 2. In selecting an antibiotic, both bacteriologic and host (patient) factors must be considered.

Bacteriologic Factors

From a bacteriologic standpoint, the agent must be active against the common respiratory pathogens and be β-lactamase-resistant. Thus, the most active agents include the newer macrolides (azithromycin and clarithromycin), doxycycline, the quinolones (ciprofloxacin, levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, and others), the advanced-generation cephalosporins (cefuroxime, cefepodoxime, cefprozil), and amoxicillin/clavulanate. Some older agents that have been used for years are not as active as these newer agents against common pathogens and do not represent good choices. Thus ampicillin and amoxicillin are of limited value because of susceptibility to bacterial β-lactamases; erythromycin is not active against *H. influenzae*; trimethoprim-sulfamethoxazole is not always active against drug-resistant pneumococci; and the earlier-generation cephalosporins are susceptible to β-lactamase and are often inactive against resistant pneumococci [15,20]. Trimethoprim-sulfamethoxazole has been used for many years as a therapy for AECB, but recent data show that penicillin-resistant pneumococci are usually resistant to trimethoprim-sulfamethoxazole and that resistance rates to

this agent by pneumococci are generally twice that seen with the macrolides [20].

Although many of the newer agents have shown efficacy in AECB, the selection of antibiotic therapy on the basis of patient subsetting has never been prospectively shown to lead to better patient outcomes than if therapy is chosen by another method. However, some studies do suggest that more complex patients frequently fail therapy with older antibiotics or with regimens that are not active against resistant and more complex organisms. In a prospective study in which patients with AECB were randomized to a quinolone therapy (ciprofloxacin) or usual care, the use of a quinolone was more cost-effective in a post-hoc analysis if the patient had at least 2 of the following 5 risk factors: moderate or severe bronchitis, at least 4 AECBs per year, illness of more than 10 years' duration, age at least 56 years, and at least 3 comorbidities [24].

A principle of antibiotic selection is to use the most focused therapy possible. Thus for the simple bronchitic, even though a quinolone is likely to be effective, a macrolide or tetracycline is preferred because they have a spectrum of activity that is focused on the core pathogens and that is not excessively broad. Among the new macrolides, azithromycin has lower minimal inhibitory concentration (MIC) values (more activity per mg of drug) against *H. influenzae* than clarithromycin, although both have been effective in the treatment of AECB patients. Another principle of antibiotic selection for AECB is that the drugs should be easily delivered to the bacteria, meaning that they should penetrate well into respiratory secretions. Antibiotic concentrations can be measured in sputum, bronchial secretions, bronchial mucosa, phagocytic cells, and epithelial lining fluid, but it is unclear which site is most relevant for patients with AECB [25]. Lipid-soluble antibiotics penetrate well into the lung, achieving levels above those present in the serum, and include the macrolides, quinolones, and tetracyclines. On the other hand, the penicillins and cephalosporins are poorly lipid-soluble and penetrate the lung only moderately well.

Patient (Host) Factors

As mentioned above, patient risk factors for specific and drug-resistant organisms and for more severe chronic illness should be considered in choosing an antibiotic. In addition, the agent chosen should maximize compliance with therapy and lead to a prolonged disease-free interval.

Patient compliance is influenced by a number of factors, including the number of drugs the patient is already taking, the frequency of medication side effects, and the ease of administration. Most patients will not reliably take an antibiotic administered more than twice daily. Many agents are now available in either once- or twice-a-day formulations. The agents previously discussed that have an appropriate

antimicrobial spectrum and that can be given once a day include azithromycin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, and doxycycline. Those that can be given twice daily include ciprofloxacin, ceftibuten, cefpodoxime, cefprozil, clarithromycin, and amoxicillin/clavulanate.


A desired outcome of therapy for AECB is to prolong the time between exacerbations. Although this endpoint has not always been examined in trials of AECB, when it has, quinolones such as ciprofloxacin have had the best results [26].

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- **Would sputum culture be helpful in targeting therapy in this patient?**
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Sputum Examination and Culture

Routine use of sputum culture in an outpatient with AECB is generally not necessary unless the patient has an exacerbation that is not responding to empiric therapy. The sputum Gram stain is not reliable for identifying the organism causing the exacerbation, since the infecting organisms in AECB illness are the same as the colonizing organisms present when the patient is stable. However, the density of organisms is increased during an exacerbation compared to when the patient is colonized and not acutely ill. In the colonized state, the patient typically has fewer than 2 bacteria per high-power field; during exacerbation, as many as 8 to 18 organisms may be seen per high-power field on Gram stain [27]. In a study of 54 patients with severe exacerbations, the amount of neutrophils and bacteria present on Gram stain was higher for the 27 patients with bacterial exacerbation than for the 27 patients with nonbacterial exacerbation; however, enough overlap existed between patients to make the use of sputum analysis unhelpful for differentiating these 2 patient groups [11]. Some investigators advocate the use of a sputum "wet prep" to look for neutrophils, but this test does not always help the physician decide whether antibiotic therapy is necessary because neutrophils are not specific for bacterial infection.

Prescription of Antibiotic and Patient Course

 Lung function testing in this patient reveals a FEV₁ of 33% of predicted normal and a PEF that has declined to 160 L/min from a baseline of 220 L/min. His FEV₁ places him in the category of complicated bronchitis at risk for *P. aeruginosa*. His age, impaired lung function, recent course of amoxicillin/clavulanate and corticosteroids, and frequency of exacerbations and the presence of congestive heart failure place him at high risk for therapy failure. The physician prescribes empiric therapy with a highly active antibiotic regimen—ciprofloxacin 750 mg twice daily for 10 days. Other therapy, including inhaled bronchodilators,

hydration with oral fluids, and a 10-day tapering course of corticosteroids is administered.

By day 3, the patient reports an improvement in his cough and dyspnea. At a follow-up visit in the office after 10 days, the patient reports that he returned to his baseline level of function by day 9.

The patient continues to do well and remains free from exacerbation for 4 months.

-
- Which antibiotic regimens are most cost-effective in the treatment of AECB?
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Cost-Effectiveness Issues

Few studies have examined the cost-effectiveness of antibiotic therapy in AECB; however, some general principles apply. Acquisition costs of antibiotics must be balanced against considerations such as accuracy of therapy, the speed at which a patient improves, whether the therapy is successful in keeping the patient out of the hospital, and whether the therapy prolongs the time between exacerbations. The cost of treatment failure is likely to be high in complex patients, as more complex patients have a limited physiologic reserve and may eventually require hospitalization if they fail an initial outpatient course of therapy.

Currently, it is estimated that patients with chronic bronchitis have on average 3 exacerbations per year, with one third of all patients having fewer than 3 episodes, one third having 3 episodes, and one third having 4 or more episodes [21]. The average cost of outpatient treatment for these exacerbations in an office, emergency department, and hospital clinic are \$74, \$76, and \$159 per exacerbation, respectively [3]. In contrast, the average cost of inpatient treatment is \$5516 per episode. Thus, antibiotic therapy that prevents hospitalization is highly cost-effective, given the large difference in the cost of care between these 2 settings. In addition, in both the outpatient and inpatient settings antibiotics account for only a small proportion of total costs (15% and 11%, respectively) [3].

One recent study [28] illustrates the value of using focused antibiotic therapy even if the acquisition cost is higher. A total of 224 exacerbations in 60 outpatients were examined, with therapy divided into first-line (amoxicillin, tetracycline, erythromycin, trimethoprim/sulfamethoxazole), second-line (cephalosporins), and third-line (amoxicillin/clavulanate, azithromycin, ciprofloxacin) agents. Patients who received first-line agents failed therapy more often than those who received third-line agents (19% versus 7%, $P < 0.05$). Moreover, those given third-line agents were hospitalized less often and had significantly longer disease-free intervals than those given first-line agents. The importance of considering a variety of

factors when defining cost-effectiveness is quite clear, as the acquisition costs of first-line agents were lower but third-line agents were more effective. Another study [29] using a pharmacoeconomic model to evaluate 1102 patients with AECB in previously reported randomized trials concluded that macrolide therapy and amoxicillin/clavulanate therapy were more cost-effective than therapy with ampicillin and older cephalosporins. It is likely that these benefits could be enhanced if therapy was chosen with patient profiles in mind.

Summary

Patients with COPD frequently develop AECB, a devastating illness if not appropriately managed. Not all patients with AECB need antibiotic therapy, but this intervention is valuable if at least 2 of 3 cardinal symptoms are present (ie, increased dyspnea, increased sputum volume, increased sputum purulence). Previous studies assumed that any antibiotic was effective for exacerbation, but this view needs to be reevaluated as the complexity of the etiologic organisms and the frequency of their resistance to antibiotics has increased. The 3 most common pathogens are *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Patients can be categorized according to likelihood of being infected with specific pathogens based on the patient's age, number of exacerbations in the past year, use of corticosteroid therapy, use of antibiotics within the past 3 months, and severity of lung function abnormalities (defined by FEV₁); the categories can be used as a basis for selecting antibiotic therapy. Some analyses show that if antibiotic therapy is focused appropriately in high-risk patients, better and more cost-effective outcomes can be achieved.

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EVALUATION FORM: The Role of Infection and Antibiotic Selection in Patients with Acute Exacerbation of Chronic Bronchitis

DIRECTIONS: Each of the questions or incomplete statements below is followed by five possible answers or completions of the statement. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following histories best describes a patient who is likely to benefit from antibiotic therapy in the setting of a known history of chronic bronchitis?
 - (A) Increased dyspnea and fever
 - (B) Increased sputum volume and increasing leg edema
 - (C) Increased sputum purulence and increased dyspnea
 - (D) Hemoptysis and increased dyspnea
 - (E) Chest pain and increasing dyspnea

2. In a patient with a history of 1 exacerbation in the past year, an FEV₁ of 65% of predicted, and no other medical problems, the most likely pathogen in acute exacerbation of chronic bronchitis (AECB) is
 - (A) *Pseudomonas aeruginosa*
 - (B) *Haemophilus parainfluenzae*
 - (C) *Escherichia coli*
 - (D) *Chlamydia pneumoniae*
 - (E) *Haemophilus influenzae*

3. The most common mechanism of resistance to ampicillin by *H. influenzae* is
 - (A) Altered penicillin-binding proteins
 - (B) Pumping of the antibiotic out of the cell (efflux pump)
 - (C) Reduced permeability of the antibiotic into the cell wall
 - (D) Production of bacterial β -lactamase enzymes
 - (E) Alteration of the nuclear DNA gyrase

4. Which of the following patient characteristics is NOT important in choosing an antibiotic for AECB?
 - (A) Degree of underlying lung disease (defined by FEV₁)
 - (B) Current smoking history
 - (C) History of antibiotic therapy in the past 3 months
 - (D) History of corticosteroid therapy
 - (E) Age

5. A patient with chronic bronchitis has on average how many exacerbations per year?
 - (A) 1
 - (B) 2
 - (C) 3
 - (D) 4
 - (E) 5



EVALUATION FORM: The Role of Infection and Antibiotic Selection in Patients with Acute Exacerbation of Chronic Bronchitis

To receive CME credit for this case study, read the case study and then answer the multiple-choice questions on page 75. Circle your answers below. Also, please respond to the four questions that follow. Then, detach the evaluation form and mail or FAX to:

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Circle your answer to the CME questions below:

- 1. A B C D E
- 2. A B C D E
- 3. A B C D E
- 4. A B C D E
- 5. A B C D E

Please answer the following questions:

- 1. In general, how do you rate the information presented in the case study?
 excellent good fair poor
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