The Value of Antibiotics and the Outcomes of Antibiotic Therapy in Exacerbations of COPD*

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COPD is the fifth leading cause of death in the United States, and acute respiratory infections account for a significant proportion of all primary care visits. Approximately one half of all exacerbations of COPD can be attributed to bacterial infection, and antibiotic therapy has been demonstrated to improve clinical outcomes and hasten clinical and physiologic recovery. The major pathogen continues to be Haemophilus influenzae, and resistance to β-lactam antibiotics such as ampicillin can be expected in 20 to 40% of isolated strains. Certain high-risk patients, in whom the cost of clinical treatment failure is high, can be identified by simple clinical criteria. Patients with significant cardiopulmonary comorbidity, frequent purulent exacerbations of COPD, advanced age, generalized debility, malnutrition, chronic corticosteroid administration, long duration of COPD, and severe underlying lung function tend to fail therapy with older drugs, such as ampicillin, and early relapse can be expected. Treatment directed toward resistant pathogens with potent bactericidal drugs may be expected to lead to improved clinical outcomes and overall lower costs, particularly if hospital admissions and respiratory failure can be prevented. Future studies examining the role of antibiotics should enroll these high-risk patients to determine if new therapies have significant clinical, quality-of-life, and economic advantages over older agents.

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COPD continues to affect 20% of the population despite public education regarding smoking; it is the fifth leading cause of death in the United States.1,2 General and family physicians frequently encounter acute bronchitis and acute exacerbations of chronic bronchitis with these illnesses accounting for approximately 14 million physician visits per year.5,4 A prevalence of chronic bronchitis and/or airflow obstruction was found in 14% of adult men and 8% of adult women in Tecumseh, Mich.5 In the United Kingdom, 25% of all primary care visits are related to respiratory disease, and more than one half of these are due to upper and lower respiratory tract infections.6 Bronchitis is associated with 28 million lost working days and 5% of deaths per year in the United Kingdom.7 In 1992, approximately 12 million prescriptions were given for lower respiratory tract infections accounting for £47.2 million ($US 77.4 million) in expenditures.8 In Europe, >80% of all lower respiratory tract infections are treated with antibiotics.9 Most physicians do not differentiate acute bronchitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia, and viral respiratory tract infections. Even with “viral” respiratory tract infections, antibiotics are given in 70% of cases.9 Based on physician surveys, at least 50% of patients with acute bronchitis will be given an antibiotic.10 The pattern of antibiotic prescribing for these infections varies from country to country, but there is no clear rationale for these antimicrobial choices.11 In the United Kingdom and France, oral penicillins predominate, while in Spain, macrolides are preferred. In Germany, tetracyclines are the first choice and in Italy, parenteral third-generation cephalosporins are the most common antibiotics prescribed. The major impact of excessive antibiotic prescribing is economic, but a corollary of this is the trend toward the emergence of resistant organisms associated with the excessive use of antibiotics.

Acute Exacerbations of Chronic Bronchitis

COPD is a progressive disease characterized by abnormal expiratory flow that is relatively stable over several months of observation.12 Chronic bronchitis is defined clinically as excessive cough, productive of sputum on most days, for at least 3 months during at least 2 consecutive years.13 Acute exacerbations of chronic bronchitis are characterized by increased cough and sputum production, increasing sputum

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purulence, and increased dyspnea. Many patients experience acute exacerbations of this chronic disease, especially during the winter season. Not all patients require antibiotics, but if an antibiotic is prescribed, it should be selected according to likely bacterial isolates. In most situations, therapy is empirical, and physicians selecting antibiotics should consider economic and clinical outcomes. Infections account for most acute exacerbations, but exposure to allergens, pollutants, or inhaled irritants may play a role. A correlation between the number of infectious flares and an accelerated decline in lung function has not been demonstrated despite the acute decline in lung function that occurs with each exacerbation. If lung function does decline acutely in patients with severe underlying lung disease, hospital admission may be necessary. Significant morbidity and mortality can be expected, especially if the patient demonstrates hypercapnia and if admission to the ICU is required.

**ROLE OF BACTERIAL INFECTION**

Antibiotics are given to most patients with acute exacerbations of chronic bronchitis, but the role of bacteria and the efficacy of antimicrobial therapy have been questioned. In patients with lower respiratory tract infections, one quarter will return to the family practitioner following a course of antibiotics for the management of persistent symptoms. Ball and coworkers demonstrated that patients with an acute exacerbation of chronic bronchitis returned to the family physician with similar frequency independent of antibiotic treatment. Sachs and coworkers could not demonstrate an additional benefit from antibiotics when given in conjunction with oral corticosteroids in patients with an acute exacerbation of mild-to-moderate asthma or COPD. However, increased numbers of bacteria and neutrophils are found in sputum during exacerbations.

An acute antibody response in serum to such bacteria and an increase in inflammatory mediators in purulent sputum can also be demonstrated. Bacterial exacerbations are usually limited to the bronchial mucosa, and many cases resolve spontaneously, which may explain in part why there are such conflicting data.

Anthonisen and coworkers, in the best designed clinical study performed to date, demonstrated that, in patients with increased dyspnea, sputum volume, and sputum purulence, broad-spectrum antibiotics (amoxicillin, trimethoprim-sulfamethoxazole, or doxycycline) led to improved clinical outcomes, fewer therapeutic failures, and a more rapid recovery of lung function compared with placebo. When they assigned treatment failures a duration of 22 days, antibiotic-treated exacerbations were shorter than those treated with placebo by >1 day. They argued that in patients with two of these symptoms, antibiotics could be justified because the rate of deterioration was higher in the placebo-treated group. If patients had only one of the three symptoms, antibiotics should not be used. A recent meta-analysis of all randomized, placebo-controlled trials of patients treated with antibiotics for acute exacerbations of chronic bronchitis concluded that a small but statistically significant improvement could be expected in antibiotic-treated patients (Table 1). An improvement of 10.75 L/min in peak expiratory flow rate was seen on average. While this is a modest overall improvement in flow rate, in patients with severe compromise of lung function, this improvement may be sufficient to avoid respiratory failure and/or ICU admission.

**BACTERIAL PATHOGENS**

In approximately two thirds of all exacerbations, a potential bacterial pathogen can be isolated from respiratory secretions. Haemophilus influenzae is

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**Table 1—Randomized Trials of Antibiotics in Exacerbations of Chronic Obstructive Lung Disease**

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Setting</th>
<th>No. of Subjects</th>
<th>Treatment</th>
<th>Main Outcome Measure</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elmes et al, 1957</td>
<td>Outpatient</td>
<td>113</td>
<td>Oxytetacycline</td>
<td>Days of illness</td>
<td>0.30</td>
</tr>
<tr>
<td>Berry et al, 1960</td>
<td>Outpatient</td>
<td>33</td>
<td>Oxytetacycline</td>
<td>Overall symptom score</td>
<td>0.71</td>
</tr>
<tr>
<td>Fear and Edwards, 1962</td>
<td>Outpatient</td>
<td>119</td>
<td>Oxytetacycline</td>
<td>Overall score by physician</td>
<td>0.31</td>
</tr>
<tr>
<td>Elmes et al, 1965</td>
<td>Inpatient</td>
<td>56</td>
<td>Ampicillin</td>
<td>Change in PEFR</td>
<td>0.49</td>
</tr>
<tr>
<td>Peterson et al, 1967</td>
<td>Inpatient</td>
<td>19</td>
<td>Chloramphenicol</td>
<td>Change in PEFR</td>
<td>0.04</td>
</tr>
<tr>
<td>Pines et al, 1972</td>
<td>Inpatient</td>
<td>149</td>
<td>Tetracycline</td>
<td>Overall physician score/change in PEFR</td>
<td>0.39</td>
</tr>
<tr>
<td>Nicotra et al, 1982</td>
<td>Inpatient</td>
<td>40</td>
<td>Tetracycline</td>
<td>Final PaO2/change in PEFR</td>
<td>0.38</td>
</tr>
<tr>
<td>Anthonisen et al, 1987</td>
<td>Outpatient</td>
<td>310</td>
<td>TMP/SMX, amoxicillin, doxycycline</td>
<td>Days of illness/change in PEFR</td>
<td>0.23</td>
</tr>
<tr>
<td>Jorgensen et al, 1992</td>
<td>Outpatient</td>
<td>262</td>
<td>Amoxicillin</td>
<td>Overall score by physicians/change in PEFR</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

*Adapted from reference 28. TMP/SMX=trimethoprim/sulfamethoxazole; PEFR=peak expiratory flow rate.
the most commonly isolated organism from sputum in patients with acute exacerbations of chronic obstructive lung disease, but other Haemophilus species, Streptococcus pneumoniae, and Moraxella catarrhalis may also be found.37 In an early study using transtracheal lung aspiration in patients with clinically stable COPD, 50% of patients were colonized with bacteria belonging to normal oropharyngeal flora and S pneumoniae and H influenzae were found in low numbers.38 Similar findings were noted during acute exacerbations using the same technique.39 Studies utilizing the protected specimen brush technique indicated that similar organisms were found during an infection-free interval, and increased numbers were associated with acute exacerbations.40-42 In a longitudinal study, exacerbations were caused by endogenous or exogenous reinfection by H influenzae.43 Persistently infected patients kept the same H influenzae strain for longer periods, and antibiotic therapy was not effective in eradicating H influenzae. β-Lactamase-mediated amoxicillin resistance can be expected in 20 to 40% of H influenzae strains in North America and Europe and in almost 100% of M catarrhalis strains.44-47 Occasional ampicillin-resistant β-lactamase-negative strains of H influenzae have also been described.47 Penicillin-resistant pneumococci are rapidly spreading, certainly in North America, and the concern of multidrug-resistant pneumococci is upon us.

**DEFINITION OF RISK FACTORS**

Patients with severe underlying lung disease with an acute exacerbation may develop acute respiratory failure. Mechanical ventilation is required in 20 to 60% of hospitalized patients, and the average hospital and ICU length of stays are long and expensive. Hospital mortality rates range from 10 to 30%.48 Factors associated with inhospital mortality include age ≥65 years, severity of respiratory and nonrespiratory organ system dysfunction, and hospital length of stay before ICU admission.49 In patients with COPD, the major determinants of 3-year survival are age and degree of airway obstruction.50 Performance status and oral steroid medication usage have also been linked to survival.51 Coexistent cardiopulmonary disease and the number of previous exacerbations have been identified as risk factors for hospitalization or returning to the physician following institution of antibiotic therapy.21 High-risk patients have been defined by a number of groups as those patients with significant impairment of lung function and having frequent exacerbations.52-54 They may be elderly, have poor performance status, and suffer from other comorbid conditions. Oral corticosteroid medication use has also been identified as a risk factor. In this targeted population, an aggressive antimicrobial approach to the treatment of exacerbations of COPD has been recommended.52-54 While this might lead to improved outcomes, randomized, controlled trials are necessary to confirm this.

**STRATIFICATION OF PATIENTS ACCORDING TO RISK FACTORS**

Therapeutic failure might be expected to lead to more hospitalizations, increased costs due to extra physician visits, prolonged absences from work, further diagnostic tests, and repeated courses of antibiotics in high-risk individuals. Routine chemotherapy fails in 13 to 25% or more of exacerbations.20,21 Stratification of patients into risk categories can identify high-risk patients and allow targeted antimicrobial therapy, particularly at resistant organisms. Treatment failure is particularly costly in these patients, since hospitalization and multiple courses of therapy are likely.14 All of the classification schemes are similar and define separate groups with increasing risk of significant impairment of health and possible adverse consequences of an acute exacerbation.

Wilson53 proposed a simple classification system, and a modification of this is shown in Table 2. In

<table>
<thead>
<tr>
<th>Table 2—Empiric Classification of Patients With Chronic Bronchitis*</th>
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<tr>
<td><strong>Baseline Clinical Status</strong></td>
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<tr>
<td>I. Acute tracheobronchitis</td>
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<tr>
<td>II. Simple chronic bronchitis</td>
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<tr>
<td>III. Complicated chronic bronchitis</td>
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<tr>
<td>IV. Chronic bronchial infection</td>
</tr>
</tbody>
</table>

*Adapted from reference 53.
patients with acute bronchitis with no underlying lung disease, the etiology is usually viral. No antibiotic is necessary for most patients. In the face of persistent symptoms, treatment with a macrolide or doxycycline is rational to eradicate potential infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*.35

The second category of patients are usually young (±60 years), have only mild-to-moderate impairment of lung function (FEV₁ ≥50% predicted), and have less than four exacerbations per year. Common organisms found are *H influenzae, S pneumoniae*, and *M catarrhalis*, although viral infections often precede bacterial superinfection. Treatment with a β-lactam is usually successful, and the prognosis is excellent. Since most of these patients respond to therapy and the consequences of treatment failure are slight, virtually any antimicrobial could be used.

Patients in the third category are older, with poor underlying lung function (FEV₁ ≤50% predicted) or only moderate impairment of lung function (FEV₁ between 50% and 65% predicted) but with concurrent significant medical illnesses (diabetes mellitus, congestive heart failure, chronic renal disease, chronic liver disease, etc.), and/or experience four or more exacerbations per year. *H influenzae, S pneumoniae*, and *M catarrhalis* continue to be the predominant organisms. In this group of patients, initial treatment failure has major implications for the patient and health-care system, including increased time lost from work and/or hospitalization. Treatment with medications directed toward resistant organisms, such as a quinolone, amoxicillin–clavulanic acid, second- or third-generation cephalosporin, or second-generation macrolide, would be expected to demonstrate cost-effectiveness since the cost of therapeutic failure in this group of patients is high.

The last group is comprised of patients who have chronic bronchial suppuration with frequent exacerbations characterized by increased sputum production, increased sputum purulence, cough, and worsening dyspnea. These individuals tend to have a chronic progressive course, and an aggressive therapeutic approach should be offered.56 Beside the usual respiratory organisms, other Gram-negative organisms, including Enterobacteriaceae and Pseudomonas species, are frequently isolated. The use of sputum cultures in this group of patients to identify potential multiresistant organisms and target specific therapy would be useful. Frequently, a quinolone is used for this group.

**PRINCIPLES OF PHARMACOECONOMIC ANALYSIS OF ANTIBIOTIC THERAPY**

Economic analyses (Table 3) examine alternative choices making explicit the assumptions and criteria by which decisions of resource allocation are made.57 There are four basic types of economic evaluation: cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). All forms of analysis must clarify the perspective from which the analysis is made. In general, a broad societal perspective should be adopted to minimize the risk that benefits or costs born by other people or sectors are ignored.58

**Cost-Minimization Analysis**

If the outcome of two treatments is identical in studies where adequate statistical power can detect clinically important differences, CMA is the most appropriate analytic technique. In this analysis, the treatment with the lowest acquisition cost should be chosen since this is the most efficient use of resources. Generic substitution of established antibiotics is an example of an appropriate use of this type of analysis.

**Cost-Effectiveness Analysis**

CEA is used when competing therapies have different clinical effectiveness, and the most relevant outcome is the same for these choices. If one therapeutic option is cheaper and has an improved

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**Table 3—Approaches Used in Pharmacoeconomic Analyses**

<table>
<thead>
<tr>
<th>Description</th>
<th>Application</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBA</td>
<td>Can compare programs with different objectives</td>
<td>Valuing benefits in monetary terms is difficult and not widely accepted</td>
</tr>
<tr>
<td>CEA</td>
<td>Can compare drugs of similar objective that use the same units of benefit</td>
<td>Cannot compare across different types of drugs/programs</td>
</tr>
<tr>
<td>CMA</td>
<td>For use when benefits of alternative drugs are the same</td>
<td>Frequently confused with CEA; difficult to establish clinically identical effectiveness</td>
</tr>
<tr>
<td>CUA</td>
<td>Allows for summing multiple dimensions of benefits into 1 scale</td>
<td>Difficult to measure utilities</td>
</tr>
</tbody>
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Mechanisms and Management of COPD
outcome, then the selection is obvious. When a treatment is more effective but also more costly, the best option demonstrates the least cost per outcome measure gained. An example of this would be using a more expensive antibiotic in a patient with an infection caused by an organism resistant to the alternative agent. The more expensive agent would eradicate the organism and cure the infection, whereas the less expensive would not.

Cost-Utility Analysis

This analysis captures the impact of a therapy on the quality of life. Quality of life has been described as domains of physical, social, and emotional health that are important to the patient. While there are many instruments capable of measuring quality of life, utility measures determine the quality of life (quality adjusted life years [QALY]) as a single number along a continuum from death (0.0) to full health (1.0). CUA measures the cost of an intervention compared with the number of QALYs gained by the application of the intervention. The preferred strategy is the selection of the therapeutic option with the lowest cost per QALY.

Cost-Benefit Analysis

This analysis measures benefit in monetary terms instead of physical terms and computes a net dollar gain or loss. CBA is not often used to compare medical therapies because of the ethical concern of placing a monetary value on health and life and how the values are assigned.

Hierarchy of Economic Studies

There are several types of economic studies, including models taking published clinical data and extrapolating the results to an economic model, retrospective analyses of large databases, “piggyback” economic studies to prearranged clinical trials, and prospective, randomized health economic trials. Economic models utilize published data to establish outcome success or failure rates with comparative antibiotics as well as published side effect profiles to determine the costs of alternative therapies. The weakness of this analysis is that published clinical efficacy studies may bear little resemblance to the real world. Particularly in the realm of antibiotics, published clinical trials of antibiotic efficacy are designed to show equivalence so the real value of new, more potent antibiotics may never be demonstrated. Examination of large databases and linking outcomes to specific usage patterns is becoming relatively common. The major hazard of this type of evaluation is that the reason for the medication usage is never explicitly stated and the linkage between the selected therapy and outcome measured may be tenuous. Economic studies attached to clinical trials are plagued by the same difficulty seen with modeling studies, that is, there is only a slim link between the results of a carefully designed efficacy study and the effectiveness of the same product when it is used in a nonrestricted manner outside a clinical trial setting. The most powerful economic analysis is a prospective, randomized economic study in which the economic questions are dealt with in a transparent manner and the effectiveness of the medication may be examined in a real-life setting.

Preventive Measures

The most important intervention in treating patients with chronic bronchitis is aggressive smoking cessation. Smoking cessation greatly reduces the rate of decline of FEV1. Previous retrospective studies have suggested similar results, and the benefit of smoking cessation is seen even in patients >60 years. Smoking cessation may result in a small initial improvement in FEV1, although this is usually not dramatic. However, smoking cessation often produces dramatic symptomatic benefits in patients with chronic cough and sputum production. Most patients have clearing of their cough and chronic sputum production often within 4 weeks of stopping smoking.

Influenza virus infection worsens the epithelial damage seen in patients with chronic bronchitis and may predispose to subsequent bacterial infection. All patients with chronic bronchitis should receive influenza vaccine annually. Morbidity and mortality from influenza are reduced by approximately 50% in vaccinated elderly patients. For elderly citizens living in the community, influenza vaccination has been demonstrated to be cost-effective, leading to reductions in hospitalization and deaths from influenza and its complications as well as direct dollar savings. The beneficial effects of pneumococcal vaccine in patients with chronic bronchitis have not been firmly established. However, current recommendations are that patients with obstructive lung disease receive pneumococcal vaccine polyvalent (Pneumovax 23) at least once in their lives and consideration be given to repeating the vaccine every 5 to 10 years. A randomized, double-blind, placebo-controlled trial of the administration of an oral immunostimulating agent containing lyophi-lized fractions of the eight most common pathogens isolated in respiratory tract infections was found to reduce the incidence of acute exacerbations of chronic bronchitis by 40% in institutionalized elderly patients.
ANTIBIOTIC TREATMENT OF ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

Most comparative trials of antibiotics with some exceptions have shown clinical equivalence.68-70 Most clinical trials were performed for registration purposes, and patients with pathogens resistant to one of the test agents were excluded from further study. Well-defined clinical trials measure efficacy of a drug but not the effectiveness in a real-world situation.71 Future studies of new antimicrobials should examine their efficacy in patients with an increased risk of true bacterial infection.14 A classification system would help select patients most likely to benefit from an antibiotic and those falling into the last two categories of Table 2 would be most appropriate.72 It is only in these patients that the potential benefits of broad-spectrum, β-lactamase stable, potent antibiotics can be demonstrated. The inclusion of patients from the first two categories can only dilute the results and minimize the advantages of more potent antibiotics. Future studies should include a well-defined, prospective economic analysis from a societal perspective, which includes a quality-of-life assessment to ascertain the cost-utility of the antibiotic in question.

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