Acute Exacerbations of Chronic Bronchitis*  
An International Comparison

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The prevalence of chronic bronchitis is between 3% and 17% in most developed countries. However, higher rates in the range of 13 to 27% are encountered in less developed areas of the world. Acute exacerbations of chronic bronchitis (AECB) have usually been defined as the presence of increases in cough/sputum, sputum purulence, and dyspnea. However, recent investigations suggest that the severity of AECB may be divided into three stages based on the history of the patient: (1) previously healthy individuals; (2) patients with chronic cough and sputum and infrequent exacerbations; and (3) persons with frequent exacerbations or more severe chronic airflow limitation. Therapy for patients with less severe AECB include older and less expensive broad-spectrum antibiotics, while newer agents are indicated for patients with the most severe stage of AECB.

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Although strikingly disparate in geography, ethnology, socioeconomic status, and other factors, the United States, Europe, Latin America, and the Asia-Pacific region have a remarkably similar incidence of chronic bronchitis (CB). Recent studies in the United States suggest a prevalence of 5.1 to 5.4% in the middle-aged to elderly population, with a lower prevalence in nonsmokers.1 Prevalence in Europe varies from 3.7% in Denmark,2 4.5% in Norway,3 6% and 6.4% in Barcelona and Valencia, Spain, respectively,4,5 and 6.7% in Sweden.6 Data are more difficult to obtain in the Asia-Pacific area but appear to be in the same range. For example, Lai and coworkers7 found 6.8% of an elderly group of Chinese living in Hong Kong to be affected, and data obtained via pharmaceutical industry research indicate the incidence, 6.9%, to be similar in Taiwan (Chan; 1997; personal communication). Figures from Indonesia are higher but do not differentiate acute bronchitis from CB or account for multiple episodes during the observation period. The age profile in an Indonesian sample of nearly 250,000 patients noted the incidence in those aged 30 to 39 years to be 15.7%; for 40 to 54 years it was 19.3%; and for ≥55 years it was approximately 6%.8 Nevertheless, the higher figures may not be so different from those reported in the United King-

dom in the early 1960s—17% of adult men9 or more recently—16.4% in elderly persons.10

Specific factors may affect the prevalence in certain countries in the southern hemisphere. Exposure to firewood or other biomass smoke during cooking may occur in up to 50% of the world’s households,11 and woodsmoke in particular is thought to be responsible for almost 50% of all cases of obstructive airways disease. Wood and straw are used for cooking with inadequate or absent ventilation. In Nepal, Pandey12 commented on the very high 18% prevalence of CB in the region and its similar frequency in both men and women. Recently, a multivariate analysis of a case control study in Colombia13 found woodsmoke to be more highly associated (odds ratio, 3.43) with development of COPD in women than either tobacco use or passive smoking (odds ratios, 2.22 and 2.05, respectively).

However, tobacco smoking is undoubtedly the most common cause of CB. Estimates of smoking prevalence range from 23% of Filipinos (Reuter’s News Service, June 24, 1995) and 26.7% in Guatemala—male to female ratio, 2:1,5,14 to 62% of adult men in Korea.15

Pathogens Associated With Exacerbations of Chronic Bronchitis

It is estimated that 50 to 75% of infective exacerbations are bacterial in origin. Studies from the northern hemisphere consistently identify Haemophilus influenzae as the major pathogen, with Moraxella catarrhalis second in importance (Table 1).

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Table 1—Prevalence of Common Respiratory Pathogens in AECB

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>H influenzae (%)</th>
<th>M catarrhalis (%)</th>
<th>S pneumoniae (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum isolates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mulder et al, 1952</td>
<td>50.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lees and McNaught, 1959</td>
<td>54.0</td>
<td></td>
<td>32.0</td>
</tr>
<tr>
<td>Gump et al, 1976</td>
<td>57.0</td>
<td></td>
<td>27.0</td>
</tr>
<tr>
<td>Davies et al, 1986</td>
<td>58.5</td>
<td>15</td>
<td>16.5</td>
</tr>
<tr>
<td>Chodosh, 1991</td>
<td>22.5</td>
<td>14</td>
<td>10.0</td>
</tr>
<tr>
<td>Lindsay et al, 1992</td>
<td>50.0</td>
<td>19</td>
<td>17.0</td>
</tr>
<tr>
<td>Ball, 1994</td>
<td>52.0</td>
<td>13</td>
<td>16.5</td>
</tr>
<tr>
<td>Sportel et al, 1995</td>
<td>35.0</td>
<td>42</td>
<td>10.0</td>
</tr>
<tr>
<td>PSB isolates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagon et al, 1990</td>
<td>30.0*</td>
<td>7</td>
<td>16.0</td>
</tr>
<tr>
<td>Monso et al, 1995</td>
<td>58.0</td>
<td>12</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*M catarrhalis not considered pathogenic until 1970s.

**PSB**=protected specimen brush specimen taken at bronchoscopy.

Including Haemophilus parainfluenzae.

### Classification

Standard definitions of CB refer to persistent cough and sputum over 2 years, but not to airflow limitation, exacerbations, or the progressive nature of the associated respiratory disability. Nevertheless, the early but definitive observations of Oswald and colleagues found 70% of patients had bronchospasm, 88% had either spasmodic or constant breathlessness, and "sells of sickness for several weeks in months" with infection playing a part in all cases. The British Medical Research Council suggested the value of a classification for both clinical and epidemiologic purposes, the need for which was reiterated by Fisher and colleagues in 1969. However, such an approach was largely ignored until the landmark study by Anthonisen and coworkers that defined exacerbations as an increase in cough/sputum, sputum purulence, and dyspnea and provided proof of the short-term efficacy of antibiotic therapy. Although frequently cited as providing guidelines for severity assessment, this study made no such claims, although an empiric severity scoring system largely based on the Winnipeg criteria was used by Allegra and colleagues in a further study with similar conclusions. However, in the late 1990s, there remain no generally accepted systems for classifying exacerbations of CB.

Specific guidelines for the evaluation of new antibiotics in acute exacerbations of CB (AECB), produced by the Infectious Diseases Society of America, incorporated standard criteria for diagnosis but none for severity. The European Respiratory Society Guidelines described three levels of severity: (1) those with mild-to-moderate exacerbations manageable on an outpatient (home-care) basis; (2) patients fulfilling the criteria for a severe acute exacerbation; and (3) those requiring intensive care. However, these guidelines are empirically based and severity criteria are largely those of supervening parenchymal infection or respiratory failure. Further, the role of antibiotics in general received no more than scant attention and choices between classes of antibiotic received no attention.

Canadian recommendations on management of CB provide more detail on AECB, the role of antibiotic therapy, stratification of patients into risk (severity) groups in addition to the classic Winnipeg symptom criteria, and empirically anticipated at least some of the factors later shown to correlate with poorer response to therapy. These include age >65 years, significant comorbid illness, FEV₁ <50% of predicted, and number of exacerbations per year. However, the resultant five-stage severity classification based on these numerous variables, although recommending a stepwise intensification of antibiotic potency for disease of increasing severity, appears unlikely to find favor with busy practitioners looking for a simple rule of thumb.

In parallel to these empiric recommendations, a number of studies have identified criteria that identify at-risk patients and that thus allow a meaningful severity classification. Unlike community-acquired pneumonia, in which the outcome variable is usually death, these studies have used return to the practitioner after therapy with no relief from or relapse of the original referring symptoms. The Winnipeg type 1 clinical criteria define a significant exacerbation but not its severity, which is predicted (in United Kingdom patients) by the numbers of exacerbations in the previous years, 4 or more having a high odds ratio for failure or relapse and significant comorbidity. Although length of history was not predictive in the latter report, a Canadian group has recently demonstrated a 10-year history of CB was associated with a poor outcome in AECB (Ronald F. Grossman, MD; 1997; personal communication). It is possible on these bases to propose a three-level staging of exacerbations (Table 2). This type of classification may allow a more rational choice of antibiotic on the basis of previous therapy, local prevalence of resistance, and other factors. The clarification in Table 2 has been accepted recently as the working basis for expert recommendations for antibiotic therapy for AECB by large consensus groups in the Asia-Pacific region and Latin America.

Analysis of outcome of treatment of exacerbations of CB and of the disease itself clearly requires more than assessments of clinical and bacteriologic response. In addition to symptom complexes, out-
comes should question the benefits to the patient’s lifestyle, activities, and sense of well-being. Such “quality of life” assessment can be defined via questionnaires that measure various aspects of the patients’ perspective of health and should be incorporated into clinical trials of newer agents to obtain valid comparisons of cost benefit.

**ANTIBIOTIC CHOICES: DEVELOPING COUNTRIES**

The criteria used to make rational choices for antibiotic use in AECB are not different from those in the affluent and more developed western countries. They include local frequencies of pathogen resistance and the availability of registered agents, which may be dramatically different in contiguous countries. However, financial influences often invalidate scientific imperatives, and patients may choose to prioritize differently from physicians. In India, casual and daily wage earners were reported to exhibit a paradoxical preference for expensive but more effective quinolone therapy. The higher costs of quinolone therapy were offset by reduction in loss of earnings and prospect of continued employment with a “sickness free” record.

Resistance rates to penicillin and amoxicillin among the principal pathogens in the Asia-Pacific region vary widely, ranging from 15% for *H influenzae* in Malaysia and Korea to 30 to 40% in Singapore, Indonesia, Thailand, Taiwan, Hong Kong, and the Philippines. Pneumococcal resistance tends to be lower in Singapore and Malaysia (10 to 20%) than elsewhere, where overall figures of 30 to 40% in Hong Kong, Korea, and Taiwan are overshadowed by hospital figures of >70% in Manila, Philippines.

Prevalence of pneumococcal resistance is lower in Latin America in general than in southeast Asia but figures reach 15 to 25% in many areas. In Latin America, the frequency of amoxicillin resistance in *H influenzae* varies dramatically between countries. Thus figures of 2.5% (Ecuador) and 10% (Colombia, Uruguay) are lower than the 25 to 30% in the general population of Argentina and Venezuela and increasing to almost 50% in hospital isolates in Guatemala.

Clearly such resistance levels compromise therapy with the basic penicillins and some oral cephalosporins. Decisions by consensus groups incorporate these factors in their recommendations. Thus, such groups in both Latin American and Asia-Pacific regions accept the use of amoxicillin for patients with few risk factors (stage 1 and stage 2) and a high probability of spontaneous recovery, although certain countries prefer to offer quinolones, macrolides, or tetracyclines as alternatives. For stage 3 patients, there is a significant consistency to the recommendations with alternative agents proposed being quinolones (first choice in Latin America, first equal in Southeast Asia), amoxicillin/clavulanic acid, azithromycin, and the more active second- or third-generation cephalosporins, eg, cefuroxime axetil and cefixime.

**MANAGEMENT GUIDELINES IN DEVELOPED COUNTRIES**

Three sets of recommendations that address the management of AECB have recently been published in more highly developed communities. Two of these guidelines, one from the United States and the other from Europe, offer a comprehensive approach to patients with COPD. Since these guidelines are very comprehensive and cover many different aspects of the management of COPD, they do not provide any in-depth approach to the use of antibiotics during exacerbations and incorporate only a general outline of therapy. Only the Canadian document is focused solely on AECB. As outlined in Table 3, these three guidelines each address four important clinical issues in patient management: (1) sputum evaluation; (2) likely responsible bacteria; (3) when antibiotics should be prescribed; and (4) primary and alternate antibiotic choices.

**Sputum Culture**

In outpatients with bronchitic exacerbations, the guidelines uniformly suggest that Gram’s stain and culture of expectorated sputum are not cost-effective and therefore not necessary; thus, antibiotic therapy should be empiric. However, sputum culture may be helpful in selected situations. The European guidelines suggest culture of the sputum to guide therapy when response to initial therapy is suboptimal. The US recommendations support sputum culture to direct therapy in more severe exacerbations, in the

**Table 2—Proposed Classification of Severity of AECB**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Background Status</th>
<th>Exacerbation Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Simple mucus hypersecretion</td>
<td>Acute tracheobronchitis in previously healthy patients</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Simple CB (2-3 yr history of cough and sputum for 2-3 mo/yr)</td>
<td>Acute increase in (a) dyspnea, (b) sputum volume, (c) sputum purulence</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Complicated CB</td>
<td>As in stage 2 plus (a) &gt;4 AECB in previous year, (b) comorbidity, (c) &gt;10-yr history of CB</td>
</tr>
</tbody>
</table>

*Modified from Ball and Wilson.*

\[<\text{CHEST / 113 / 3 / MARCH, 1998 SUPPLEMENT}\]
Table 3—International Guidelines for Management of AECB

<table>
<thead>
<tr>
<th>Topic</th>
<th>Europe(^{21})</th>
<th>United States(^{26})</th>
<th>Canada(^{22})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial sputum analysis</td>
<td>Not necessary</td>
<td>Not necessary</td>
<td>Only with FEV(_1) (&lt;50%) pred, age &gt;65 yr, or ≥4 exacerbations/yr</td>
</tr>
<tr>
<td>Sputum analysis in other cases</td>
<td>When response to initial therapy is poor</td>
<td>In severe exacerbations, recent antibiotics, nursing home residence, or hospital admission</td>
<td>With lack of improvement or deterioration</td>
</tr>
<tr>
<td>Responsible bacteria</td>
<td>Streptococcus, Haemophilus, Moraxella; increasing Staphylococcus and resistance</td>
<td>Streptococcus, Haemophilus, Moraxella</td>
<td>Streptococcus, Haemophilus, Moraxella; increasing resistance</td>
</tr>
<tr>
<td>When to treat</td>
<td>Sputum purulence in an exacerbation</td>
<td>Change in sputum color or consistency in an exacerbation</td>
<td>≥2 of: increased cough/sputum, sputum purulence, dyspnea</td>
</tr>
<tr>
<td>Initial antibiotics</td>
<td>Amoxicillin, tetracycline derivatives, amoxicillin/clavulanic acid</td>
<td>Tetracycline, doxycycline, amoxicillin, erythromycin, trimethoprim-sulfamethoxazole, cefaclor</td>
<td>Aminopenicillin, tetracycline, trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Secondary antibiotics</td>
<td>Newer cephalosporin, macrolide, quinolone</td>
<td>Broad-spectrum penicillin, cephalosporin</td>
<td>Cephalosporin (second or third generation), amoxicillin/clavulanic acid, newer macrolide, quinolone</td>
</tr>
</tbody>
</table>

face of recent prior antibiotic administration, when the patient resides in a nursing home, and when the patient is sufficiently ill to require hospital admission; the Canadian guidelines similarly recognize the importance of Gram’s stain and culture in a more complicated subset of patients.

**Causative Bacteria**

All three publications recognize the importance of bacteria such as *Streptococcus pneumoniae*, *H influenzae*, and *M catarrhalis*. Although the problem of antibiotic resistance is recognized by the European and Canadian guidelines, this issue is not addressed by the Americans. Discussion on the increasing incidence of Staphylococcus as a cause of exacerbations and increasing antibiotic resistance of Haemophilus and of Streptococcus are prominent in the European publication, and the Canadian guidelines indicate the potential for resistance in more complicated patients including those with more than four exacerbations per year and thus prior antibiotic therapy. However, both the European and US documents suggest that knowledge of local bacterial resistance patterns and local experience in antibiotic efficacy are helpful in guiding initial antibiotic selection.

**When To Use Antibiotics**

Although detailed guidelines for when to use antibiotics are not provided, the Europeans indicate that administration of antibiotics is appropriate for patients with purulent sputum, and further suggest that patients may be given a prescription for antibiotics for early initiation when appropriate signs or symptoms develop. The US guidelines focus more on exacerbations, which though not defined are implied to indicate increasing dyspnea. A change in sputum color or consistency during an outpatient exacerbation, and in all cases in which patients are hospitalized for an exacerbation, are suggested indications for antibiotics in the United States. The Canadian guidelines, following the results of Anthonisen et al., recommend antibiotics with two or more of the symptoms of increased cough/sputum, sputum purulence, and dyspnea.

**Antibiotic Choices**

Since most exacerbations of CB occur in patients who have not had multiple recurrences and who may not even have airflow limitation, inexpensive, older antibiotics are preferred. The US guidelines suggest a broad set of initial antibiotic choices, including tetracycline, doxycycline, amoxicillin, erythromycin, trimethoprim-sulfamethoxazole, or cefaclor. Both the Europeans and Canadians agree that less expensive antibiotics are sufficient and recommend amoxicillin and tetracycline derivatives as initial antibiotics. The Europeans also recommend amoxicillin/clavulanic acid as an initial choice.

European guidelines suggest alternate antibiotics, including newer cephalosporins, macrolides, and quinolones. The US recommendations for alternate antibiotics are broad-spectrum penicillins and cephalosporins. The Canadians recommend similar alternate antibiotics not only for patients who have suboptimal initial response but also suggest these agents are appropriate as a first choice in patients with more complicated disease.

The repetitive demonstration of the equivalence of
new agents, eg, the macroazalides and quinolones, to ampicillin-amoxicillin despite their clear microbiological and kinetic advantages, is generally not reflected in the initial antibiotic choices. This is perhaps best reflected by a recent draft of the British Thoracic Society COPD Guidelines that appear to provide no severity assessment for exacerbations and that suggest the use of amoxicillin or tetracycline should increased dyspnea, sputum volume, and purulence be present. This fails to recognize the prevalence of bacterial resistance in the United Kingdom, even though lower than elsewhere, the marginal pharmacokinetics of such agents in respiratory tissues, and the frequency of therapeutic failure of such therapy in even mild exacerbations managed at home.27

In summary, the published guidelines from the more developed countries fail to consistently and clearly identify when to treat patients with antibiotics and when to use alternate antibiotics in patients with more complicated disease. The Canadian recommendations present a provocative, though clinically untested, classification of severity of the underlying disorder that may prove a useful guide to treatment.

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