Outcome Predictors in Bronchitis*

Robert Wilson, MD

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A
cute bronchitis in previously fit people is a common condition often occurring at the time of an upper respiratory tract infection that "goes down onto the chest." Viruses are common etiologic agents, although *Mycoplasma pneumoniae* may be a frequent cause during epidemics, and recent evidence suggests *Chlamydia pneumoniae* can also produce this syndrome. Secondary bacterial infections may occur due to *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae*. Symptoms are relatively mild and the condition is usually self-limiting, although a condition of bronchial hyperresponsiveness can develop for weeks after an apparently mild attack.

Chronic bronchitis is defined by common consensus as daily production of sputum for at least 3 months in 2 consecutive years. Patients with chronic bronchitis are a heterogeneous group owing to the range of severity of the condition and its common association with airflow obstruction, which may or may not be reversible, and emphysema. Three separate but continuous entities have been defined: simple chronic bronchitis, chronic or recurrent mucopurulent bronchitis, and chronic obstructive bronchitis. Exacerbations are common to all three groups, but their cause may be difficult to identify and might include viral infection, environmental pollutants, allergic responses, and bacterial infection. The cause of an exacerbation may be multifactorial, so that viral infection or levels of air pollution may exacerbate preexisting inflammation in the airways, which in turn may predispose to secondary bacterial infection. Understanding the basic mechanisms underlying these events may be germane in predicting the likely outcome of an exacerbation.

**PATHOPHYSIOLOGY**

The hypersecretion of mucus in chronic bronchitis is due to hypertrophy of the submucosal glands and increase in the numbers of goblet cells in the epithelium at the expense of ciliated cells. Epithelial metaplasia also occurs, and together with abnormalities of ciliary function and mucus rheology, these changes lead to impairment of mucociliary clearance, an important first-line defense mechanism of the airways. Bronchoalveolar lavage and biopsy studies have provided evidence for the accumulation of inflammatory cells in airways of subjects with chronic bronchitis. Lavage shows that the principal intraluminal cellular change is an increased number of neutrophils, whereas bronchial biopsy specimens have shown increased numbers of lymphocytes, macrophages, eosinophils, and mast cells. The discrepancy between lavage and biopsy findings may be due to the rapid migration of neutrophils through the mucosa into the airway lumen, where they are attracted by host (eg, C5a, LTB4, and IL8) and bacterial-derived chemotaxins. Recruitment of inflammatory cells to sites of mucosal inflammation involves leukocyte-endothelial adhesion molecules, which are expressed on endothelial cells as ligands for leukocyte cell receptors. Two adhesion molecules, E-selectin and intercellular adhesion molecule-1 (ICAM-1), are important for the recruitment of neutrophils and eosinophils. There is increased expression of E-selectin on vessels and ICAM-1 on basal epithelial cells in patients with chronic bronchitis with airflow obstruction, which probably reflects ongoing inflammation occurring in the absence of any clinical exacerbation.

Nontypable *H influenzae*, *S pneumoniae*, and *Moraxella catarrhalis* are the most common bacterial species isolated from sputum during infective exacerbations of chronic bronchitis. These species form part of the normal upper respiratory tract flora and have relatively low virulence. They often persist in the airways of patients with severe chronic bronchitis, even between exacerbations. Their presence in the lower respiratory tract reflects the failure of the host defenses and could be ascribed either to the ability of the bacteria to overcome host defenses or to a deficiency in one or more of the clearance mechanisms. The question concerns the relative contribution of host and microbial determinants, and for bronchial infections, it is probably the permissive role of reduced host defenses that is most important.

**A VICIOUS CIRCLE HYPOTHESIS OF BACTERIAL INFECTION IN CHRONIC BRONCHITIS**

A variety of circumstances, singularly or in concert, may create permissive circumstances that allow bacteria in the respiratory tract to increase in number and spread. This may involve, for example, viral infection or inhalation of airborne pollutants, which cause
inflammation and perturb mucosal defenses. Bacterial toxins (eg, ciliotoxins or IgA1 proteases) contribute to the infection by overcoming residual host defenses and damaging the epithelium,\(^4\) and the variability of the surface of nontypable \textit{H influenzae} may allow the bacterium to escape immune surveillance.\(^9\) Bacterial multiplication stimulates an inflammatory response, which becomes chronic if it fails to clear the infection. Neutrophils traffic into the bronchial tree and during phagocytosis spill proteinase enzymes and toxic oxidants that are found in purulent sputum.\(^10\) There is an increasing awareness in the pathogenesis of a wide range of acute and chronic lung disorders, that it is not only tissue injury by foreign material (eg, cigarette smoke) or invading microorganisms that is important, but that the host response to such agents can contribute to the disease process. Proteinases and toxic oxidants generated by activated phagocytes are unable to discriminate between microbial pathogens and host cells, and therefore have the potential to damage innocent bystander cells. Injury to bystander cells is usually minimized by the transient, self-limiting nature of the acute inflammatory response and the protection provided by biologic defense systems that neutralize it. If, however, the inflammatory response is ineffectively downregulated or persists, leading to hyperacute or chronic activation of neutrophils, then the defenses may be overwhelmed and host tissues damaged. Human neutrophil elastase and the oxidants hydrogen peroxide and hypochlorous acid stimulate mucus production, impair ciliary function, and damage epithelial cells.\(^11-13\)

The bronchial defenses are therefore impaired during an exacerbation, both by bacterial products and the host inflammatory response. In addition, new sites for bacterial adherence to the epithelium, which were previously unavailable, may be exposed by epithelial damage.\(^14\) Inflammatory processes may continue in the bronchial wall after the exacerbation has clinically ended\(^5\) and low numbers of bacteria may persist in the mucosa.\(^8\) Therefore, for a period following an exacerbation, these factors make another exacerbation more likely to occur. This susceptibility will continue until the inflammation resolves and the host defenses repair themselves. Each further exacerbation makes the next more likely, leading to a vicious circle of events (Fig 1).

Evidence is lacking that bacterial infections contribute to long-term decline in lung function of patients with chronic bronchitis. There have been four prospective studies addressing this issue that have been reviewed recently,\(^19\) and only one concluded that more frequent episodes of infection correlated with a more rapid decline in lung function. However, the mechanisms outlined above may well contribute to the outcome of an exacerbation. Intuitively, the more severe the airway damage, the more impaired the bronchial defenses are likely to be, and the more likely an exacerbation is to occur; and the worse the lung function in the patient's stable state, then the more serious a further deterioration during an exacerbation is likely to be.

\textbf{Are Some Patients Prone to Recurrent Infections?}

It has been suggested recently that some patients with chronic bronchitis are prone to recurrent acute exacerbations, while others with apparently similar degrees of lung damage are not.\(^15\) In this study, there were no differences in age, sex, or symptoms in the two groups, and the smoking history was greater in the noninfection-prone group. In a second-year follow-up study, nearly 80\% of patients maintained their original classification. If these observations\(^15\) are correct, then comparisons between "infection-prone" and "infection-resistant" patients with similar severity of chronic bronchitis may be very informative.

Patients may harbor the same genetic strain of \textit{H influenzae} for long periods,\(^8,9\) and if a particular strain had particular properties that made it more virulent, this could influence clinical outcome. However, it seems more likely that the characteristics of the host, rather than the bacterium, will be more important in influencing susceptibility to infection. Bacterial adherence to the respiratory mucosa may be an important part of the pathogenesis of infection. The number or accessibility of receptors for bacterial adhesins on the mucosa may be influenced by factors other than simple lung damage,\(^16\) and this may therefore influence bacterial colonization. Some immunologic or other host defense deficiency could be present making patients susceptible to infection, and this possibility deserves further investigation. We have found that some patients who have been considered to have smoking-related chronic bronchitis, and who have been referred because of recurrent infections, have unsuspected bronchiectasis when investigated by high-resolution thin-section CT. The condition of the airways might be more important than overall lung damage, because patients with pure emphysema do not usually suffer frequent bronchial infections.
OUTCOME PREDICTORS IN CHRONIC BRONCHITIS

Studies of community-acquired pneumonia have identified various criteria predictive of severity of disease and response to antibiotic therapy. These have permitted the development of prognostic indices and scoring systems based on statistical analysis. However, severity classifications based on the symptoms of exacerbations of chronic bronchitis thus far produced have been largely empirical and have not been validated by clinical trials. An example of one such attempt at classification is given in Table 1.

Acute infective exacerbations of chronic bronchitis are mucosal infections and will, in most cases, resolve spontaneously. The inclusion of many patients with poorly defined disease of relatively minor severity, in which the spontaneous remission rate is high, may explain why the great majority of comparative clinical trials demonstrate no significant differences between standard comparators and new treatments. Placebo-controlled trials are rarely performed, usually on ethical grounds. The continued performance of such studies, largely for the purposes of registration of new antibiotics, is unlikely to prove valuable in assessing the role of antibiotics in the management of acute exacerbations of chronic bronchitis. Some authors have raised doubts about the potential for, and reliability of, assessments of antibiotic therapy in chronic bronchitis because of its heterogeneous nature, diffuse symptoms, and difficulties in defining clinical response both in the short and long term. The lack of uniformity in entry criteria to clinical trials in chronic bronchitis also invalidates the use of meta-analysis of multiple publications. More precise definitions of exacerbations of chronic bronchitis and a classification of severity based on easily evaluable clinical parameters are therefore required. This was suggested by Fisher et al in 1969, but very little progress has been made during the succeeding 25 years.

Anthonisen and colleagues, in perhaps the best study of the use of antibiotics to treat exacerbations of chronic bronchitis performed so far, showed significant benefits for antibiotic therapy compared with placebo in patients judged to have moderate to severe exacerbations on the basis of increased dyspnea, sputum production, and sputum purulence. In the same study, no benefit from antibiotics was demonstrated for milder exacerbations involving only one of these clinical parameters. In a more recent study, approximately 25% of patients presenting to their general practitioner with a lower respiratory tract infection returned because they had not recovered. These data suggest that there is a subgroup of patients with a prognosis less promising. If these patients could be identified, then their treatment could receive special attention, and they could be enrolled into clinical trials as they have disease of sufficient severity to detect differences in efficacy between new treatments in comparison with placebo or conventional management.

We have recently carried out a large community-based study to determine whether features of history, presenting symptoms, or findings on examination could be identified that were predictive of failure to recover from an acute exacerbation of chronic bronchitis. Patients were studied by their family practitioners at presentation with what was considered an infective exacerbation and, following treatment, at any return visit during the next 4 weeks. A total of 471 patients were studied by 124 general practitioners throughout the United Kingdom during the winter of 1992 to 1993. Only practices using a computerized data-collecting system were used, which allowed verification of current and past history. The median age of the patients was 68 years, 56.3% were male, and 82% were smokers or ex-smokers. The median duration of symptoms was 12 years. All patients gave a history of daily cough and sputum production, and 92% had significant obstruction of the airways. In 57.5%, this was considered to be moderate or severe. Thirty-eight percent of patients had coexistent cardiopulmonary disease, which included ischemic heart disease and cor pulmonale. There was a large range in the number of exacerbations during the last 12 months, from nil to 12 or more. The group divided roughly into thirds: 37.4% had less than three exacerbations in the last 12 months, 30.8% had three or four, and 31.8% had more than four.

Clinical features at presentation included a moderate or severe increase in dyspnea (45%) and airflow obstruction (41%), and increased sputum production (77%). The sputum was mucopurulent or purulent in 66% of cases and there were abnormal auscultatory signs in 81%, but only 12% were pyrexial.

The general practitioners were allowed to give whatever treatment they wished. Unfortunately, in retrospect, although the antibiotic was recorded if prescribed, ancillary treatment such as corticosteroid therapy was not. Antibiotic therapy was prescribed for 80% of patients at presentation, the most frequently prescribed class being the β-lactams. Of the 56 patients (13%) who returned to the physician with a chest problem during the 4-week follow-up period, 9 were referred to hospital, and 2 died of respiratory causes.

Table 1—Empirical Classification of Patients With Chronic Bronchitis

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<thead>
<tr>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Previously healthy patient with postviral tracheobronchitis</td>
</tr>
<tr>
<td>2</td>
<td>Simple chronic bronchitis</td>
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<tr>
<td>3</td>
<td>Chronic bronchitis &quot;plus&quot; airflow obstruction and/or other medical problems, eg, diabetes, heart failure, and/or elderly</td>
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<tr>
<td>4</td>
<td>Chronic bronchial sepsis: daily purulent sputum production, usually have bronchietasis</td>
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Both univariate and multivariate analyses were performed to investigate all possible combinations of historic and clinical variables that might predict these outcomes.

None of the clinically observable variables, either singly or in combination, were found to predict failure to recover and return to the general practitioner. No advantage was demonstrated to receiving an antibiotic.

Eleven of 79 (13.9%) patients not prescribed an antibiotic returned with a respiratory problem, compared with 45 of 344 (13.1%) given an antibiotic. Only one of the nine patients referred to hospital at the second visit had not received an antibiotic at the first visit. The only features that predicted failure to recover were historic. Coexistent cardiopulmonary disease was found to be a risk factor for returning with a chest problem and for being referred to hospital. The number of previous exacerbations was a risk factor for returning with a chest problem. The higher the number of exacerbations, the higher the odds of returning with a chest problem. Having considered all possibilities, the best predictive combination of failure to recover from an exacerbation was a history of coexistent cardiopulmonary disease and more than four exacerbations in the last 12 months. The sensitivity for this combination of variables was 75% and the specificity was 47%.

The placebo-controlled study by Anthonisen and colleagues\(^\text{21}\) showed that patients with chronic bronchitis with increased dyspnea and sputum production and purulent sputum benefit from antibiotic therapy. Our study has shown that unless patients have a history of coexistent cardiopulmonary disease and frequent exacerbations, they are likely to recover from the exacerbation whatever their treatment. This concurs with the opinion of Murphy and Seth\(^\text{9}\) that most infections in chronic bronchitis are mucosal infections that will resolve spontaneously. Conversely, it also suggests, as do the studies of Taylor et al\(^\text{15}\) and Macfarlane et al\(^\text{20}\) that there is a subgroup of patients who are less likely to recover from an exacerbation. This group of patients should be identified for careful clinical management, investigation of underlying mechanisms, and should be included in clinical trials. In addition, as our results of antibiotic therapy have shown, placebo-controlled trials in defined populations should be encouraged.

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