Clinical studies in chronic bronchitis: a need for better definition and classification of severity


The definition of chronic bronchitis is generally accepted to be daily production of sputum for at least 3 months in 2 consecutive years. Cigarette smoke is the main aetiological agent, and causes increased numbers of goblet cells in the epithelium and hypertrophy of submucosal glands. Increased mucus production together with impaired mucociliary clearance lead to the characteristic productive cough (Wilson, 1988). However, patients who fall under the umbrella of the clinical definition of chronic bronchitis are a very heterogeneous group. This is due to the range of severity of the condition, its common association with airflow obstruction, which may or may not be reversible, and emphysema, and a variable susceptibility to infective exacerbations (Medical Research Council, 1965; Ball et al., 1995).

Acute exacerbations of chronic bronchitis (AECB) are common, but their cause may be difficult to identify and might include viral infection, environmental pollutants, allergic responses and bacterial infection. The cause may be multifactorial, so that viral infection or levels of air pollution may exacerbate bronchitis, which in turn may predispose to secondary bacterial infection.

Antibiotics are commonly prescribed during exacerbations, but evidence that they appreciably alter the outcome is lacking. In one study, 13-9% of patients not prescribed an antibiotic failed to recover compared to 13-1% of those receiving an antibiotic (Ball et al., 1995). In another recent study (Macfarlane et al., 1993), approximately one-quarter of patients presenting to their general practitioner with a lower respiratory tract infection returned, usually because of incomplete recovery. Antibiotics may only benefit subgroups of patients that have, so far, not been well characterized.

Non-typable Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis form part of the normal upper respiratory tract flora and are the commonest bacterial pathogens isolated from sputum during exacerbations (Davies et al., 1986; Aldons, 1990; Basran et al., 1990; Chodosh, 1991; Lindsay, Scorer & Carnegie, 1992). They may persist in the lower airways of patients with severe disease between exacerbations (Groeneveld et al., 1988). Their presence in the lower respiratory tract reflects both the failure of the host defences and the ability of the bacteria to evade clearance. There are host and microbial determinants of any infectious process, but for bronchial infections it is probably the permissive role of the impaired host defences which is most important. The precise contribution of bacterial infection to the pathogenesis of AECB remains controversial. The finding that potential pathogens such as H. influenzae and S. pneumoniae are isolated in increased numbers during exacerbations than in quiescent periods (Fisher et al., 1969), and the demonstration of an antibody response to the sputum isolate (Musher et al., 1983), argue strongly in favour of an active role. It has been suggested that repeated or chronic bacterial infection initiates and perpetuates a cycle of airway damage based upon stimulation of inflammatory mechanisms by bacteria and their products (Cole & Wilson, 1989; Murphy & Sethi, 1992). However, only one of four prospective studies has concluded that more frequent episodes of infection correlated with a more rapid decline in lung function (Murphy & Sethi, 1992).

Studies involving small numbers of patients have provided conflicting evidence of the efficacy of antibiotics (Berry et al., 1960; Pines et al., 1968) or the lack of it (Elmes et al., 1965; Petersen et al., 1967; Nicotra, Rivera & Awe, 1982; Leading Article, 1987). AECB due to bacterial infection are mucosal infections and will, in the majority of cases, resolve spontaneously (Murphy & Sethi, 1992). The inclusion of many patients with poorly defined disease of relatively minor severity, in which the spontaneous remission rate is high, may explain the great majority of comparative clinical trials which demonstrate no significant differences between standard comparators and
Table. Suggested criteria to be incorporated in protocols of antibiotic studies in chronic bronchitis

<table>
<thead>
<tr>
<th><strong>At entry to determine severity</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms: increased dyspnoea, increased sputum production, purulent sputum (Anthonisen et al., 1987)</td>
<td></td>
</tr>
<tr>
<td>Past history: coexistent cardiopulmonary disease, three or more infective exacerbations in last twelve months (Ball et al., 1995)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>To determine efficacy of antibiotic</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiology of sputum one week after cessation of antibiotic (mandatory)</td>
<td></td>
</tr>
<tr>
<td>Speed of recovery of specific symptoms</td>
<td></td>
</tr>
<tr>
<td>Time until next infective exacerbation</td>
<td></td>
</tr>
<tr>
<td>Need for subsequent therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Desirable additional parameters</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td>Pharmacoeconomic analysis</td>
<td></td>
</tr>
</tbody>
</table>

New antibiotics which, on microbiological and pharmacokinetic grounds might be thought to be superior. The continued performance of such studies, largely for the purpose of new product registration and licensing, is unlikely to be valuable in assessing the role of antibiotics in the management of AECB. Placebo-controlled trials are rarely performed, usually on ethical grounds. Twenty-five years ago it was suggested that more precise definitions of AECB were needed, together with a classification of severity based on easily evaluable clinical parameters (Fisher et al., 1969). There has been very little progress since that time, and indeed the recently published guidelines for the evaluation of new antibiotics for respiratory tract infections contain no reference to the severity of an AECB (Chow et al., 1992).

Anthonisen and colleagues (1987) showed significant benefits for antibiotics compared with placebo in patients judged to have moderate to severe exacerbations on the basis of increased dyspnoea, sputum production and sputum purulence. In the same study, no benefit from antibiotics was demonstrated for milder exacerbations involving only one of these symptoms. We have recently carried out a large community-based study to determine whether features of past history, presenting symptoms or findings on examination, could be identified that were predictive of failure to recover from an AECB (Ball et al., 1995).

Although clinical symptoms and findings on examination indicated that most patients in the study were suffering a moderate to severe exacerbation, none of the clinically observable variables, either singly or in combination, was found to predict failure to recover. The only two features that predicted failure to recover were historical. Co-existent cardiopulmonary disease was a risk factor for failing to recover and for being referred to hospital. The number of previous exacerbations in the last 12 months was a risk factor, and the higher the number of exacerbations, the higher the odds of not recovering.

Chronic bronchitis remains a common cause of morbidity and mortality. We believe that it is time to take a fresh look at AECB, both from a basic science and clinical perspective. The role of air pollution requires further investigation, because the concentrations at which airborne pollutants increase symptoms is not fully known, nor is there adequate information on synergy between various pollutants and the effect of other factors such as temperature. Recent studies have begun to apply cell and molecular biology techniques to biopsy specimens. For example, the adhesion molecules E-selectin and intercellular adhesion molecule-1 (ICAM-1), that are involved in the control of recruitment of neutrophils and eosinophils to the airway, are upregulated in patients with chronic obstructive bronchitis outside exacerbations (Di Stefano et al., 1994).

This might predispose such patients to an exaggerated inflammatory response following an insult to the airways. Modern imaging techniques could be used to classify patients, and to define disease processes. Thin-section high-resolution CT scanning has, in our experience, shown that some patients with chronic bronchitis who suffer recurrent infections also have cylindrical bronchiectasis.

Patients enrolled into clinical studies should satisfy entry criteria to ensure that the disease is of sufficient severity to make it possible to detect differences in efficacy between treatments, and new parameters to judge efficacy.
might also be introduced (Table). We would suggest that patients enrolled into trials of new compounds for registration purposes should all have increased purulent sputum production and dyspnoea as suggested by Anthonisen et al. (1987); a history of frequent exacerbations and coexistent cardiopulmonary diseases as defined by Ball et al. (1995) could also be included when assessing new agents against standard comparators. We would also encourage placebo controlled studies be undertaken under carefully observed conditions.

ROBERT WILSON*  
GLENN TILLOTSON  
PETER BALL  
*Host Defence Unit,  
Department of Thoracic Medicine,  
Royal Brompton National Heart and Lung Institute,  
Emmanuel Kaye Building,  
Mansrero Road,  
London SW3 6LR;  
*Bayer plc, Bayer House,  
Strawberry Hill,  
Newbury,  
Berkshire RG13 1JA;  
Infectious Diseases Dept,  
Victoria Hospital,  
Kirkcaldy,  
Fife KY2 5AX, UK  
*Tel: +44-(171)-351-8337; fax: +44-(171)-351-8338.

References


Petersen, E. S., Esmann, V., Honoke, P. & Munkner, C (1967) A controlled study of the effect of