The Role of Infection in COPD*

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Clinical studies of acute exacerbations of COPD are difficult because of the heterogeneous nature of COPD, diffuse symptoms that can vary spontaneously, and difficulties in defining clinical response both in the short and long term. The role of bacterial infection, and thus use of antibiotics, in COPD is controversial. The available evidence shows that bacterial infection has a significant role in acute exacerbations, but its role in disease progression is less certain. Upper respiratory tract commensals, such as nontypable Haemophilus influenzae, cause most bronchial infections by exploiting deficiencies in the host defenses. Some COPD patients are chronically colonized by bacteria between exacerbations, which represents an equilibrium in which the numbers of bacteria are contained by the host defenses but not eliminated. When an exacerbation occurs, this equilibrium is upset and bacterial numbers increase, which incites an inflammatory response. Neutrophil products can further impair the mucosal defenses, favoring the bacteria, but if the infection is overcome, symptoms resolve. However, if the infection persists, chronic inflammation may cause lung damage. About half of exacerbations involve bacterial infection, but these patients are not easy to differentiate from those who are uninfected, which means that antibiotics have to be given more often than is strictly necessary. Further research is needed to characterize those patients in whom bacterial infection has a more important role.

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COPD is a general term used to cover a variety of abnormalities that often coexist: chronic bronchitis, emphysema, and peripheral airway disease. Acute exacerbations of COPD (AECOPD) are common, particularly during the winter months.¹ There are several reasons why clinical studies of AECOPD, and studies of the role of infection in particular, are difficult to perform. During an AECOPD, patients complain of breathlessness, wheeze, cough, and sputum production, which are the same symptoms that they have to a lesser extent in a stable phase. Furthermore, patients are usually recruited for clinical studies opportunistically when they present with an AECOPD, so little is known about their state preexacerbation. For these reasons, it can be difficult to judge the adequacy of recovery following an episode and the extent of any persisting deterioration, and it may not be possible to differentiate the changes that occur during an exacerbation from spontaneous variations that occur in COPD, particularly since resolution of symptoms without treatment is quite common. Long-term deterioration in FEV₁ occurs so slowly as not to be a useful outcome measure. Traditionally, studies have concentrated on improvement in symptoms as judged by diary cards recording symptoms, sputum microbiology, and measurement of peak flow and FEV₁ at enrollment and after treatment. These measures are crude and may underestimate the impact of AECOPD on health status. Another feature of AECOPD that complicates studies is that there are a number of different causes that include viral infection, environmental pollution (including cigarette smoke), allergy, and bacterial infection. These may occur together; for example, a prior viral infection may predispose to a secondary bacterial infection. There is also a wide spectrum of severity, largely depending on the extent of the underlying airflow obstruction and emphysema. Therefore, patients with AECOPD are a very heterogeneous population, but this is often ignored in clinical trials, and the type of patient enrolled is poorly defined.

The benefit of antibiotic therapy in AECOPD has been debated for 30 years or more.²,³ Placebo-controlled studies involving small numbers of patients have provided conflicting evidence of the efficacy of antibiotics⁴,⁵ or the lack of it.⁶-⁸ Only one of four prospective studies has concluded that more frequent episodes of infection correlated with a more rapid decline in lung function.⁹ Many other studies have been performed comparing the efficacy of different antibiotics in AECOPD. Most of these studies have shown equivalence, perhaps because they were performed for the purposes of new product registration and licensing, in which case this outcome was desirable. These studies have contributed very little to our understanding of the role of

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infection in COPD.\textsuperscript{10} Many studies have included patients with poorly defined disease, sometimes one suspects of minor severity, or included patients with different pathologies, \textit{eg}, asthma. Sachs et al\textsuperscript{11} found that when patients with mild-to-moderate COPD were given antibiotics together with a short course of oral prednisolone, antibiotics did not accelerate recovery or reduce the number of relapses. However, few of the patients had positive sputum Gram's stains and culture results, and asthmatics were included in the study, as were patients with increased breathlessness but no sputum production. Although this study makes an important point about patients with mild-to-moderate exacerbations, the relevance of the results for patients with true bronchial infections is uncertain.

\section*{Bacteriology}

The three major bacterial pathogens isolated during bronchial infections are nontypable \textit{Haemophilus influenzae}, \textit{Moraxella catarrhalis}, and \textit{Streptococcus pneumoniae}.\textsuperscript{3,9} These species all form part of the commensal flora in the nasopharynx and are less virulent, in the usually accepted sense of the word, than those causing pneumonia. Klingman et al\textsuperscript{12} did not find any evidence that acquisition of a new strain of \textit{M catarrhalis} led to an exacerbation. They studied \textit{M catarrhalis} isolated from regularly obtained sputum samples of bronchiectasis patients and characterized strains by restriction fragment length polymorphisms. Patients were colonized by a particular strain for several months, and acquisition of a new strain did not correlate with changes in clinical status or antibiotic use. Bronchial infections occur in patients with abnormal airways who have reduced host defenses. The pathogenic mechanisms of bacterial infection in COPD need to be looked at differently than pneumonia. They should be considered in the context of how they facilitate persistence in the bronchial tree and include toxins that impair mucociliary clearance, enzymes that break down local immunoglobulin, exproducts that alter immune effector cell function, adherence to mucus and damaged epithelium, and ways the bacteria have of avoiding immune surveillance.\textsuperscript{13} Bronchial infections usually remain confined to the mucosa, and many of them will resolve spontaneously without the need for treatment.\textsuperscript{9} When bacterial infection persists, it usually reflects the severity of the impairment of the lung defenses rather than the virulence of the microorganism. The damage to lung tissue caused by the host inflammatory response to chronic bacterial infection may be more important than the damage caused by the bacteria themselves.\textsuperscript{9,13}

A history of purulent sputum production suggests bacterial infection, but other conditions, such as asthma and postnasal rhinorrhea, may give the same history. Sputum Gram's stain is frequently not performed, but it can help confirm that the sample is from the lower respiratory tract, that there is inflammation present containing neutrophils and not eosinophils, and it may also suggest a bacterial pathogen. Sputum culture results are complicated by contamination from the upper respiratory tract, and even when sputum cultures are carefully performed, results do not always concur with protected specimen brush samples taken from the bronchial tree.\textsuperscript{14}

\section*{Antibiotics and Acute Exacerbations of COPD}

Antibiotics are usually prescribed by physicians and demanded by patients for AECOPD.\textsuperscript{15,16} Although academics continue to be uncertain about their benefit, patients do not seem to be in any doubt. This is one aspect of the discussion that has not received sufficient attention, since it suggests that antibiotics make patients with AECOPD feel better (for whatever reason), even if at the moment we have difficulty measuring why this might be. Antibiotics prescribed for lower respiratory tract infections cost 47.2 million pounds in the United Kingdom in 1992.\textsuperscript{15} However, this is only a fraction of the financial burden of AECOPD to the economy and health service resources. Twenty-five million working days are lost in the United Kingdom per year due to the disease and its exacerbations.\textsuperscript{3} Failure of empiric therapy leads to extra costs arising from repeated consultations, investigations, ancillary and social services, and most costly of all, admission to hospital. In two large community studies carried out recently, between 13\% and 25\% of patients with chest infections required a second consultation due to inadequate resolution of their symptoms.\textsuperscript{15,16}

There are a large number of antibiotics available to treat AECOPD. Standard agents such as amoxicillin, ampicillin, tetracycline, erythromycin, and co-trimoxazole have been joined by newer agents with either a better spectrum of activity \textit{in vitro} and/or better pharmacokinetics. These include quinolones, azalides, antibiotics incorporating a \(\beta\)-lactamase inhibitor, and second- and third-generation cephalosporins. During the last 10 years, there has been a steady rise in the frequency of \(\beta\)-lactamase production by \textit{H influenzae} and \textit{M catarrhalis}, and more recently, strains of penicillin-resistant pneumococci have emerged.\textsuperscript{3} There is some evidence that widespread use of antibiotics has led to increased resistance,\textsuperscript{17} which has in turn led to increased prescription of the new antibiotics mentioned above.
No consensus has developed as to the appropriate use of antibiotics in AECOPD or about the choice of a particular antibiotic. This uncertainty could have a number of undesirable consequences. First, new antibiotics may be prescribed inappropriately, leading to unnecessary expense and development of bacterial resistance. Second, standard antibiotics may be given to all AECOPD patients because they are cheaper, and new antibiotics could be reserved exclusively for failures. Although the evidence that new antibiotics are more effective is not that strong, there are logical reasons why they might be used for more serious bronchial infections if these patients can be identified. New antibiotics are more expensive, but they could be cost-effective in severe COPD patients in whom failure rates are higher and hospital admission is more likely. Lastly, publicity about antibiotics being overprescribed, leading to increased bacterial resistance, may cause antibiotic treatment to be withheld at the detriment of patients.

Current guidelines on the management of COPD from the United States and Europe pay scant attention to antibiotics. The American Thoracic Society recommends that antibiotics be used if there is evidence of infection. The Society suggests that fever, leukocytosis, and changes in the chest radiograph will help differentiate those patients needing antibiotics. This advice fails to recognize that most decisions are taken empirically, that a minority of patients with bacterial bronchial infection have fever (which is more common with viral infection or pneumonia), and that chest radiograph changes are unusual in simple AECOPD. The European Respiratory Society recommends antibiotics if purulent sputum is present and suggests standard antibiotics as first line, followed by sputum culture if these fail. Failure of standard antibiotic therapy is unlikely to be too important in previously well patients with good respiratory function in whom spontaneous recovery is usual, but in patients with severe COPD, failure might have more serious consequences, and therefore, there should not be any delay in prescribing effective treatment. The inadequacy of the present guidelines is due to the lack of information that can be gained from the clinical studies performed to date. Further studies are required, and new approaches should be taken to determine the role of infection so that better guidelines can be written.

Evidence That Bacterial Infection Has a Significant Role in AECOPD

Although sputum culture is not an exact science, it has provided important information about the isolation of potential bacterial pathogens in AECOPD. The importance of *H influenzae* and *S pneumoniae* was recognized in the classic work of May. Lees and McNaught isolated these bacteria singly or jointly in the sputum of 75% of bronchitic patients. *H influenzae* was isolated more commonly, being found in 54% of subjects who had bacteria present, compared with pneumococci in 32% and mixed cultures of these two pathogens in 11%. More recently *M catarrhalis* has been recognized as a potential pathogen. Numerous studies have reported these three bacteria as the most common isolates from sputum, usually with *H influenzae* being the most frequent. Recent studies have reported the isolation of other Gram-negative bacteria, such as *Pseudomonas aeruginosa*, from patients with more severe COPD.

There is ample evidence to support the role of bacterial infection in the pathogenesis of cystic fibrosis and bronchiectasis. In these conditions, bacterial infection is chronic and as well as causing acute exacerbations, it is the major determinant of long-term disease progression. Chronic infection stimulates a “vicious cycle” during which the host inflammatory response promotes continued infection and tissue damage. The multiplication and spread of bacteria in the bronchial mucosa stimulate the host to mount an inflammatory response. If this fails to clear the bacteria and the infection continues, the inflammatory response becomes chronic. Large numbers of activated neutrophils are attracted into the airway by host and bacterial chemotactic factors. Activated neutrophils do not differentiate between bacteria and bystander lung tissue. They spill proteinase enzymes and reactive oxygen species, and because of the large numbers of neutrophils present, lung defenses, such as antiproteinases, are overwhelmed. High levels of biologically active neutrophil elastase have been measured in the sputum of chronically infected patients. Proteinase enzymes and reactive oxygen species cause epithelial damage and stimulate mucus production. These changes impair mucociliary clearance and encourage continued bacterial infection. Neutrophil elastase in secretions attracts more neutrophils into the airway by inducing production of the powerful chemoattractant interleukin 8 by epithelial cells, and impairs phagocytosis by destroying antibody and cleaving complement receptors from neutrophils and complement components from bacteria. Hence, a self-perpetuating cycle of events develops that damages lung structural proteins as well as airway epithelium.

The same cellular mechanisms that operate in cystic fibrosis and bronchiectasis also operate in COPD, but the inflammation is less severe and...
in this condition, neutrophils are stimulated by other factors, including cigarette smoke. The role of bacterial infection in most COPD patients may be confined to a proportion of acute exacerbations. However, some patients with COPD seem to be prone to bacterial infections.\textsuperscript{30} One explanation might be that the residual inflammation and damage to local host defenses that follow an infective exacerbation leaves the patient susceptible to a further infection, until the host defenses have had time to recover, particularly if bacterial eradication is incomplete. In a selected group of patients with smoking-related COPD referred to our clinic because of recurrent infections, unsuspected cylindrical bronchiectasis was shown by high-resolution thin-section CT.\textsuperscript{31} These studies suggest an overlap between COPD and bronchiectasis, which is also suggested by the isolation of \textit{P. aeruginosa} from some patients.\textsuperscript{24} However, susceptibility to infection does not seem to be predicted by lung function,\textsuperscript{30} and further research needs to be carried out to characterize those COPD patients in whom bacterial infection has a more important role. In this subgroup, inflammation stimulated by recurrent infections may contribute to disease progression.

Some COPD patients are chronically colonized by bacteria between exacerbations,\textsuperscript{32} and bacterial numbers then increase during exacerbations.\textsuperscript{33} Bronchoscopic protected brush sampling showed that 10 of 40 COPD patients were colonized by bacteria when in a stable state. During an exacerbation, the percentage of infected samples increased to 50\%. The bacteria isolated were predominantly the three species described above, both in the stable state and during exacerbations, with bacterial numbers greater during exacerbations.\textsuperscript{34} Bacterial colonization in the stable state represents an equilibrium in which the number of bacteria present in the bronchial tree is contained by the host defenses, but not eliminated. When an exacerbation occurs, this equilibrium is upset and bacterial numbers increase, which incites an inflammatory response. This usually occurs because of a change in the host rather than the virulence of the bacterium, for example, following a viral infection, which allows the bacteria to escape from their containment by the host defenses.\textsuperscript{13}

Fagon et al\textsuperscript{14} studied 54 patients with severe AECOPD who had increased cough, sputum production, and breathlessness which led to hypercapnic respiratory failure and artificial ventilation. A bronchoscopic protected brush sample was taken from the bronchus with the most secretions, and it showed bacterial infection in half of the cases. However, neither clinical features nor other investigations differentiated the infected group from the noninfected group. This important study suggests that although antibiotics are not needed in every case, they have to be prescribed for seriously ill patients because those patients in whom infection is not present cannot be confidently identified.

A meta-analysis of nine placebo-controlled antibiotic trials in COPD by Saint et al\textsuperscript{35} established a small but significant benefit from antibiotic therapy. Although no microbiological investigations were performed in the large study carried out by Anthonisen et al,\textsuperscript{36} the authors showed significant benefits from antibiotics compared with placebo in patients judged to have moderate-to-severe AECOPD on the basis of having at least two of three cardinal symptoms: 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.

**Classification of Patients With Bronchial Infections**

Several authors have argued that there is an immediate need for guidelines on antibiotic use in COPD.\textsuperscript{31,37-39} Several attempts at guidelines have been made that have resulted in broadly similar recommendations. Although the recommendations have been hampered inevitably by the lack of present knowledge, they have taken a practical approach that seems to be logical and can be used in primary care. It must be emphasized, however, that the concepts on which the guidelines are based have not yet been verified by clinical trials. An example is given in Table 1. This approach seeks to classify patients in a way that can be recognized by general practitioners, restricts antibiotic use to those who are most likely to benefit, and reserves new antibiotics for patients with more severe disease. Patients with postviral tracheobronchitis or simple chronic bronchitis have absent or mild-to-moderate underlying lung disease, and therefore, have relatively intact host defenses. Spontaneous resolution of symptoms is common in these patients, and often antibiotics are not required. Standard antibiotics can be given if patients have purulent sputum production, particu-

<table>
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<tr>
<td>1. Previously healthy patient with postviral tracheobronchitis</td>
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<tr>
<td>2. Simple chronic bronchitis; mild airflow obstruction</td>
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<tr>
<td>3. Chronic bronchitis; significant airflow obstruction; associated risk factors</td>
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<td>4. Chronic bronchial suppuration (bronchiectasis)</td>
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larly if they are also short of breath.\textsuperscript{36} Class 3 and 4 patients (Table 1) have more severe lung disease and bronchial infections in these patients are less likely to resolve spontaneously because the host defenses are more severely impaired. They represent more serious illness because these patients have lung function that is already impaired and/or they have a comorbid condition, eg, heart failure or diabetes that may be aggravated by the exacerbation. A number of risk factors have been identified for poor outcome in AECOPD (Table 2),\textsuperscript{15,36,40-45} but these do not necessarily reflect risk factors for poor outcome from an infective exacerbation. This is important since antibiotics would be expected only to help infected cases.

Prescott et al\textsuperscript{40} studied 214 cases in which COPD was an underlying or contributory cause of death. From the presence or absence of increased mucus, purulent mucus, fever, leukocytosis, and infiltration on a chest radiograph, death was classified as either due to pulmonary infection or not. As in previous studies, there was a strong inverse relationship between ventilatory function and COPD-related mortality. However, chronic mucus hypersecretion was found only to be a significant predictor of COPD-related death with pulmonary infection.

Bronchial infections probably arise from the population of bacteria colonizing the patient, either in the nasopharynx or the bronchial tree, at the time of an AECOPD.\textsuperscript{9,12,13,32} For this reason, recent exposure to antibiotics makes the incidence of infection by antibiotic-resistant strains more likely. New antibiotics have advantages compared with older agents in that resistance is less common, and some of them, e.g, quinolones and azalides, penetrate very well into the bronchial mucosa. They should be reserved for class 3 and 4 patients, where in some patients they may be used first line. They may also be considered for class 2 patients who fail to respond to treatment with standard antibiotics, although the diagnosis of a bronchial infection should be reconsidered since asthma commonly masquerades as a bronchial infection not responding to antibiotic therapy.

**Table 2—Risk Factors That Contribute to Poor Outcome in AECOPD**

<table>
<thead>
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<th>Risk Factor</th>
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<tr>
<td>Lung function</td>
<td>36,40,41</td>
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<tr>
<td>Blood gases</td>
<td>41</td>
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<tr>
<td>Comorbid conditions</td>
<td>15,41,42</td>
</tr>
<tr>
<td>Frequent exacerbations</td>
<td>15,41,42</td>
</tr>
<tr>
<td>Mucus hypersecretion</td>
<td>40</td>
</tr>
<tr>
<td>Continued smoking</td>
<td>40,43</td>
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<tr>
<td>Body mass index</td>
<td>44</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>45</td>
</tr>
<tr>
<td>Age</td>
<td>36,40</td>
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**Future Studies**

Some authors have raised doubts about the potential for, and reliability of, assessments of antibiotic therapy in COPD because of its heterogeneous nature, diffuse symptoms, and difficulties in defining clinical response both in the short and long term.\textsuperscript{46} However, as outlined above, this is such an important issue that I believe we must take a fresh look at AECOPD, both from a basic science and clinical perspective.\textsuperscript{10} The studies of Monso et al\textsuperscript{34} and Fagon et al\textsuperscript{14} have made an excellent start to defining the role of bacterial infection in AECOPD. Recent studies have also begun to apply cell and molecular biology techniques to COPD. For example, the adhesion molecules E-selectin and intercellular adhesion molecule-1, which are involved in the recruitment of neutrophils and eosinophils to the airway, are upregulated in some COPD patients between exacerbations.\textsuperscript{47} This might predispose such patients to an exaggerated inflammatory response following bacterial infection.

Health-related quality of life (HRQL) measures are increasingly being used in clinical trials to provide a standardized global assessment of the patient’s health status and to quantify the size of health gain from therapy. Such measures bring together a number of different aspects of a disease and give a robust summary of a patient’s symptoms and their impact on daily life and activities. Disease-specific measures for respiratory conditions have been shown to be valid, reproducible, and sensitive to change.\textsuperscript{48} HRQL questionnaires have not yet been applied to antibiotic studies in COPD. In a recent study, we found that the frequency of infective exacerbations was a major determinant of the quality of life of patients with bronchiectasis.\textsuperscript{49} Peak flow rate, spirometry, and the presence or absence of a positive sputum culture have all been shown to be good predictors of HRQL.\textsuperscript{49-51} Furthermore, it has also been shown that a physician’s assessment of a patient’s health status can be very different from the patient’s own perception of how he or she feels.\textsuperscript{52} HRQL questionnaires could be used to supplement traditional outcome measures, since it may be just as important to measure an antibiotic’s effect on the patient’s overall health status as it is to measure its effect on sputum microbiology.

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