Exacerbations of Chronic Obstructive Pulmonary Disease

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Summary

Exacerbations of chronic obstructive pulmonary disease (COPD) cause morbidity, hospital admissions, and mortality, and strongly influence health-related quality of life. Some patients are prone to frequent exacerbations, which are associated with considerable physiologic deterioration and increased airway inflammation. About half of COPD exacerbations are caused or triggered primarily by bacterial and viral infections (colds, especially from rhinovirus), but air pollution can contribute to the beginning of an exacerbation. Type 1 exacerbations involve increased dyspnea, sputum volume, and sputum purulence; Type 2 exacerbations involve any two of the latter symptoms, and Type 3 exacerbations involve one of those symptoms combined with cough, wheeze, or symptoms of an upper respiratory tract infection. Exacerbations are more common than previously believed (2.5–3 exacerbations per year); many exacerbations are treated in the community and not associated with hospital admission. We found that about half of exacerbations were unreported by the patients, despite considerable encouragement to do so, and, instead, were only diagnosed from patients’ diary cards. COPD patients are accustomed to frequent symptom changes, and this may explain their tendency to underreport exacerbations. COPD patients tend to be anxious and depressed about the disease and some might not seek treatment. At the beginning of an exacerbation physiologic changes such as decreases in peak flow and forced expiratory volume in the first second (FEV1) are usually small and therefore are not useful in predicting exacerbations, but larger decreases in peak flow are associated with dyspnea and the presence of symptomatic upper-respiratory viral infection. More pronounced physiologic changes during exacerbation are related to longer exacerbation recovery time. Dyspnea, common colds, sore throat, and cough increase significantly during prodrome, indicating that respiratory viruses are important exacerbation triggers. However, the prodrome is relatively short and not useful in predicting onset. As colds are associated with longer and more severe exacerbations, a COPD patient who develops a cold should be considered for early therapy. Physiologic recovery after an exacerbation is often incomplete, which decreases health-related quality of life and resistance to future exacerbations, so it is important to identify COPD patients who suffer frequent exacerbations and to convince them to take precautions to minimize the risk of colds and other exacerbation triggers. Exacerbation frequency may vary with the severity of the COPD. Exacerbation frequency may or may not...
increase with the severity of the COPD. As the COPD progresses, exacerbations tend to have more symptoms and take longer to recover from. Twenty-five to fifty percent of COPD patients suffer lower airway bacteria colonization, which is related to the severity of COPD and cigarette smoking and which begins a cycle of epithelial cell damage, impaired mucociliary clearance, mucus hypersecretion, increased submucosal vascular leakage, and inflammatory cell infiltration. Elevated sputum interleukin-8 levels are associated with higher bacterial load and faster FEV₁ decline; the bacteria increase airway inflammation in the stable patient, which may accelerate disease progression. A 2-week course of oral corticosteroids is as beneficial as an 8-week course, with fewer adverse effects, and might extend the time until the next exacerbation. Antibiotics have some efficacy in treating exacerbations. Exacerbation frequency increases with progressive airflow obstruction; so patients with chronic respiratory failure are particularly susceptible to exacerbation. Key words: chronic obstructive pulmonary disease, COPD, exacerbation. [Respir Care 2003;48(12):1204–1213. © 2003 Daedalus Enterprises]
Using the median number of exacerbations as a cut-off point, we classified COPD patients in the East London study into “frequent” and “infrequent” exacerbators. Quality-of-life scores were significantly worse among the frequent exacerbators in all three of the St George’s Respiratory Questionnaire component scores: symptoms, activities, and impacts (Fig. 1). This suggests that exacerbation frequency is an important determinant of health status with COPD patients, and health status is now regarded as one of the important COPD outcome measures. Further analysis of factors predictive of frequent exacerbations included daily cough and sputum and frequent exacerbations in the previous year. Patients who were frequent exacerbators in one year were likely to have a higher exacerbation frequency in the following years. A previous study of acute infective exacerbations of chronic bronchitis found that one of the factors predicting exacerbation was the number of exacerbations in the previous year, though that study was limited to exacerbations presenting with purulent sputum and no physiologic data were available during the study.

Physiologic changes (eg, decreases in peak flow and forced expiratory volume in the first second [FEV1]) immediately prior to exacerbation are generally small and not useful in predicting exacerbations, but larger decreases in peak flow are associated with dyspnea and the presence of symptomatic colds. Larger physiologic changes at exacerbation are related to longer exacerbation recovery time. Symptoms of dyspnea, common colds, sore throat, and cough increased significantly during the prodromal phase, and this suggests that respiratory viruses may be important triggers of exacerbations (Fig. 2). However, the prodrome of COPD exacerbation is relatively short and not useful in predicting onset. As colds are associated with longer, and thus more severe exacerbations, a COPD patient who develops a cold may be prone to more severe exacerbations and should be considered for early therapy at onset of symptoms.

**COPD Exacerbations and Disease Progression**

The median time to recovery of peak flow was 6 days and time to recovery from symptoms was 7 days, but at 35 days the peak flow had returned to normal in only 75% of exacerbation patients, whereas at 91 days a conservative calculation showed that 7.1% of exacerbation patients had not returned to baseline lung function. The reasons for incomplete recovery of lung function and incomplete recovery from symptoms are not clear but may involve inadequate treatment or persistence of the causative agent. The incomplete recovery of lung function after an exacerbation means that the patient may not regain his or her stable lung function, which may contribute to the decline in lung function with time, which is characteristic of COPD patients. Further evidence of incomplete exacerbation recovery was recently provided by a study of patients with chronic bronchitis; recovery of quality-of-life scores was incomplete after infective exacerbations, especially when the exacerbations occurred during the study follow-up.

Early data from the cohort studies by Fletcher et al suggested that exacerbations have no effect on lung function decline in COPD. However, recent evidence suggests

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**Fig. 1. Effect of exacerbation frequency on quality of life, measured with the St George’s Respiratory Questionnaire (SGRQ), the components of which are symptoms, activities, impacts, and total. The clear bars represent patients who suffered infrequent exacerbations (≤2 in the previous year). The black bars represent patients who suffered frequent exacerbations (3–8 in the previous year). The difference between frequent exacerbators and infrequent exacerbators is significant (p < 0.002) for each SGRQ component. (Adapted from data in Reference 2.)**
that exacerbations may have an important effect on COPD disease progression. One recent study suggested that among smokers exacerbations are associated with more lung function decline.\textsuperscript{11} In another study, in which patients were divided into frequent and infrequent exacerbators, the patients with histories of frequent exacerbation had faster FEV\textsubscript{1} decline than patients who had had infrequent exacerbations (Fig. 3).\textsuperscript{12} Further calculations suggested that the contribution of exacerbation to lung function decline was of the order of 25\%, and thus cigarette smoking is still the most important factor in COPD disease progression.

These findings emphasize the importance of targeting COPD exacerbations to reduce disease progression and particularly to detect patients who are frequent exacerbators. Further long-term studies are required to evaluate the effect of exacerbations on disease progression in COPD and to ascertain which groups of patients are at particular risk of disease progression. It is also necessary to study the effect of exacerbation on disease progression at different stages of the disease.

Patients with alpha-1 antitrypsin deficiency are a good group by which to evaluate the mechanisms of COPD, as the annual decline in lung function is accentuated among alpha-1 antitrypsin deficiency patients. Dowson et al conducted longitudinal studies of patients who have the PiZ phenotype and emphysema and found that, over the whole range of FEV\textsubscript{1} values, there is no relationship between FEV\textsubscript{1} decline and exacerbations.\textsuperscript{13} However, among patients with FEV\textsubscript{1} above 35\% of predicted (who had the highest decline in FEV\textsubscript{1}), a significant relationship was found between lung function decline and exacerbation frequency. In addition, the number of exacerbations over the study period for the patient group as a whole was also related to the vital capacity and the transfer factor. These data provides further evidence of the role of exacerbation, which is associated with increased inflammation and COPD disease progression.

**Longitudinal Changes of COPD Exacerbation**

There is little information in the literature about how exacerbation frequency changes in patients and whether the nature of the exacerbations alter. There is some evidence, mainly from subgroup analyses in pharmacologic
studies, that exacerbation frequency increases with disease severity. However, the exact nature of that relationship is not known along the spectrum of disease severity, nor whether there is a critical level of lung function at which exacerbation frequency increases. The East London study cohort was followed over a 6-year period and there was no overall change in exacerbation frequency, but that may have been because exacerbations do not increase linearly with FEV1 decrease or because therapy may have helped stabilize the exacerbation rates of those patients.

Further analysis shows that, over time, exacerbations have more symptoms and take longer to recover from. As the number of symptoms and physiologic changes at exacerbation are related to exacerbation recovery time, those findings suggest that exacerbations become more severe over time. As airway inflammation is progressive, it is likely that exacerbations are associated with more inflammatory changes and thus will become more severe. We also found that, with time, exacerbations are more likely to be associated with more purulent sputum, and this also suggests increasing inflammatory load with time at exacerbation. Thus, patients with more severe COPD need to be educated about the nature and consequences of COPD exacerbations, and they should be encouraged to present early to health care professionals.

Airway Inflammation at Exacerbation

COPD exacerbations are associated with airway inflammation, though there has been little information available on the nature of inflammatory markers, especially when studied close to an exacerbation, because performing bronchial biopsy during exacerbation is difficult in patients with moderate to severe COPD. The relationship of airway inflammatory changes to symptoms and physiologic changes at exacerbation is also an important factor to consider.

In one study, in which biopsies were performed at exacerbation in patients with chronic bronchitis, increased airway eosinophilia was found, though the patients studied had only mild COPD. At exacerbation there were more modest increases observed in neutrophils, T lymphocytes, and cells positive for tumor necrosis factor alpha. Sputum induction allows study of these patients at exacerbation, and sputum induction is safe and well-tolerated with COPD patients. In the prospectively followed cohort of patients in the East London study who had moderate-to-severe COPD, inflammatory markers in induced sputum were related to symptoms and physiologic variables at baseline and exacerbation. There was a relationship between exacerbation frequency and sputum cytokines; baseline measurements of sputum from patients who suffered frequent exacerbations had more interleukin-6 (IL-6) and IL-8 than did sputum from patients who suffered infrequent exacerbations (Fig. 4), although there was no relationship between cytokines and baseline lung function. As discussed below, exacerbations are triggered by viral infections, especially by rhinovirus, which is the cause of the common cold. Rhinovirus has been shown to increase cytokine production in an epithelial cell line, and thus repeated viral infection may lead to upregulation of cytokine airway expression.

Increases in various inflammatory markers have been found at COPD exacerbation, including inflammatory cytokines, IL-6, IL-8, endothelin-1, the neutrophil chemoattractant leukotriene b4 (LTB4), and neutrophil elastase. We found that induced sputum IL-6 levels were higher when exacerbations were associated with symptoms of the common cold (see Fig. 4). However, there was considerable variability in inflammatory markers during exacerbation, suggesting marked heterogeneity in the degree of the inflammatory response during exacerbation.

Bhowmik et al found that there was no increase in the eosinophil count in induced sputum at exacerbation, even though the patients in that study were sampled early during exacerbation, at the onset of symptoms. Compared to the study by Saetta et al, in which the patients had mild COPD, the patients in the Bhowmik et al study had more severe and irreversible airflow obstruction (mean FEV1 39% of predicted), and the majority of the patients were taking inhaled steroids, which could have reduced eosinophils. It is also possible that the inflammatory response at exacerbation is different in nature in patients with moderate-to-severe COPD than in patients with milder COPD.

In the study by Bhowmik et al, patients were followed with daily diary cards, so the inflammatory response could be related to exacerbation recovery. There was no rela-
tionship between the degree of inflammatory cell response during exacerbation and the duration of symptoms and lung function changes. Induced sputum markers taken 3–6 weeks after exacerbation showed no relationship to exacerbation changes, though the study may have been underpowered for a detailed analysis of airway markers and the time course of the exacerbation. Thus, to date, levels of induced sputum markers at exacerbation do not predict the subsequent course of the exacerbation and do not appear to be useful in the prediction of exacerbation severity.

In patients with alpha-1 antitrypsin deficiency there is some evidence of greater inflammatory load at the start of the exacerbation, with higher elastase activity, lower sputum alpha-1 antitrypsin, and lower secretory leukoprotease inhibitor than in COPD patients who do not have alpha-1 antitrypsin deficiency. In that study, biochemical markers were reduced by 3 days after antibiotic therapy and took a variable time to return to baseline. However, there was no difference between the 2 treatment groups in the time course of the reduction in inflammatory markers, though there were considerable differences in the levels of the inflammatory markers. Although there is a suggestion that exacerbations may be more severe in patients who have alpha-1 antitrypsin deficiency, peak flow changes with therapy did not differ, which suggests that response to therapy is similar in the 2 patient groups. Whether the increased inflammatory response at exacerbation in patients who have alpha-1 antitrypsin deficiency plays a part in the accelerated FEV₁ decline requires further study with a larger number of patients.

Etiology of COPD Exacerbation

COPD exacerbations have been associated with a number of etiological factors, including infection and pollution episodes. COPD exacerbations are frequently triggered by upper respiratory tract infections, and these are commoner in the winter months, when there are more respiratory viral infections in the community. It is also possible that patients are more susceptible to exacerbations in the winter months, as lung function in COPD patients shows small but significant decreases with reduction in outdoor temperature during the winter months. COPD patients have also been found to have more hospital admissions during times of more environmental pollution. However, in asthma, common pollutants, especially oxides of nitrogen and particulates, may interact with viral infection (rather than acting alone) to precipitate asthma exacerbation, and a similar mechanism may occur in COPD.

Viral Infections

Viral infections are an important trigger for COPD exacerbations. Recent studies have shown that around half of COPD exacerbations are associated with viral infections and that the majority of these were due to rhinovirus. Viral exacerbations were associated with symptomatic colds and prolonged recovery. However, both Seemungal et al. and Rohde et al. showed that rhinovirus can be recovered from sputum more frequently than from nasal aspirates at exacerbation, suggesting that wild type rhinovirus can infect the lower airway and contribute to inflammatory changes at exacerbation. We also found that exacerbations associated with the presence of rhinovirus in induced sputum had larger increases in airway IL-6 levels, suggesting that viruses increase the severity of airway inflammation at exacerbation. This finding is in agreement with the data that respiratory viruses produce longer and more severe exacerbations and have a major impact on health care utilization. Systemic inflammatory markers were also increased where there was evidence of airway viral infection.

The major receptor for rhinoviruses is intercellular adhesion molecule (ICAM-1), which is located on the airway epithelial cells. There is some evidence that in COPD there may be upregulation of ICAM-1 on airway cells, and this would suggest an increased susceptibility to rhinovirus infection. However, there is no evidence to date that COPD patients have more viral infections, though the inflammatory effect of the rhinoviral infection may be greater in COPD patients, and this may lead to the characteristic lower airway symptoms of an exacerbation. In addition to the effects on cytokine secretion, rhinovirus can also stimulate mucus production from the airway epithelium and thus potentiate the sputum production during a COPD exacerbation.

Bacterial Infection

Between 25 and 50% of COPD patients have lower airway colonization by bacteria, especially noncapsulated Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. This colonization has been related to the severity of COPD and cigarette smoking. The presence of bacteria in the lower airways of COPD patients implies a breach of host defense mechanisms, which sets up a vicious cycle of epithelial cell damage, impaired mucociliary clearance, mucus hypersecretion, increased submucosal vascular leakage, and inflammatory cell infiltration. The airway bacterial load in the stable state is associated with airway inflammatory markers and, thus, increased bacterial colonization is associated with greater airway inflammation. We have recently shown that airway bacterial colonization is variable in patients when samples are taken about 1 year apart and that changes in airway bacterial load are related to the FEV₁ decline. Those COPD patients who exhibited more changes in the nature of bacterial colonization suffered from faster de-
clines in lung function. Higher sputum IL-8 levels were associated with higher bacterial load and faster decline in FEV\textsubscript{1} and, thus, the bacteria increase airway inflammation in the stable state and this in turn may increase disease progression.

If bacterial colonization is related to increased airway inflammation, then colonization may be associated with increased exacerbation frequency, as we have recently shown.\textsuperscript{34} Lower airway bacterial colonization may also modulate the character of the exacerbation, and we have also recently shown that patients with a higher exacerbation frequency show increased bacterial colonization. Patients who were colonized with \textit{H. influenzae} had greater sputum purulence associated with the exacerbation and also had a longer time to recovery of peak flow, though this latter difference between colonized and noncolonized patients did not reach statistical significance.\textsuperscript{34} Thus the presence of bacterial colonization in COPD patients may have an influence both on the exacerbation frequency and on the character and severity of exacerbations.

At exacerbation there is an increased chance of detecting bacteria, especially if the exacerbation is associated with the presence of purulent sputum.\textsuperscript{35} Recently Sethi et al suggested that isolation of a new bacterial strain in COPD patients who were regularly sampled was associated with an increased risk of an exacerbation, though this does not conclusively prove that bacteria are direct causes of exacerbations.\textsuperscript{36} With antibiotic therapy, bacterial load and airway inflammation decreases, and the rate of resolution of the airway inflammatory changes is related to the clearance of bacteria from the sputum.\textsuperscript{37}

Atypical bacteria have been proposed as causes of COPD exacerbations, especially \textit{Chlamydia pneumoniae}.\textsuperscript{38} However, it is not clear whether \textit{C. pneumoniae} is a true pathogen at exacerbation or an innocent bystander. In our cohort study we found no relationship between \textit{C. pneumoniae} detection and airway inflammatory markers.\textsuperscript{39} However, \textit{C. pneumoniae} can also be detected in blood monocytes, and further investigation is required to evaluate its role in the pathogenesis of exacerbation.

**Issues in Management of COPD Exacerbations**

There are 2 separate issues in the management of COPD exacerbation: therapy and prevention. Both of these have improved as a result of better understanding of the causes and mechanisms of COPD exacerbations.

A number of randomized, controlled studies have indicated that oral corticosteroids can be beneficial at COPD exacerbation.\textsuperscript{40–42} A course of oral corticosteroids at exacerbation increases the rate of recovery from the exacerbation. Studies have shown that a 2-week course is as beneficial as an 8-week course and avoids the adverse effects of longer-term steroid therapy.\textsuperscript{42} Increased bronchodilator and combination therapy is also used at exacerbation to reduce dyspnea, though few studies are available to show that this approach is beneficial.\textsuperscript{43,44} There is also little evidence for greater long-term benefits of exacerbation therapy. Seemungal et al conducted a cohort study of the effect of prednisolone on COPD exacerbations diagnosed and treated in the community, and found that exacerbations treated with steroids were more severe and associated with larger decreases in peak flow.\textsuperscript{9} The treated exacerbations also had a longer recovery time to baseline for symptoms and peak flow, and the rate of peak flow recovery was faster in the prednisolone-treated group. An interesting finding was that steroids significantly prolonged the median time from the day of onset of the initial exacerbation to the next exacerbation from 60 days in the group not treated with prednisolone to 84 days in the patients treated with prednisolone.\textsuperscript{9} If short-course oral steroid therapy at exacerbation does prolong the time to the next exacerbation, it could be an important way to reduce exacerbation frequency in COPD patients.

Exacerbations of COPD often present with increased sputum purulence and volume, and antibiotics have traditionally been used as first-line therapy in such exacerbations. However, viral infections may be the triggers in a substantial proportion of infective exacerbations, and antibiotics are used in these cases for the consequences of secondary infection. A study investigating the benefit of antibiotics in over 300 exacerbations demonstrated a greater treatment success rate in patients treated with antibiotics, especially if their initial presentation was with all the 3 major symptoms: increased dyspnea, sputum volume, and purulence.\textsuperscript{5} Patients with mild COPD obtained less benefit from antibiotics. A randomized, placebo-controlled study of the value of antibiotics in patients with mild obstructive lung disease in the community concluded that antibiotics did not accelerate recovery or reduce the number of relapses.\textsuperscript{45} A meta-analysis of trials of antibiotic therapy for COPD identified only 9 studies of adequate duration and concluded that antibiotic therapy offered a small but significant outcome benefit in exacerbations.\textsuperscript{46} With the advent of newer antibiotics that have more specific profiles against bacteria, the effectiveness may be greater.

There has been recent interest in the potential role of macrolide antibiotics for COPD, as they have been shown to have beneficial anti-inflammatory activity in patients with cystic fibrosis and obliteratorive bronchiolitis. Macrolides have also been shown to inhibit airway cytokine production stimulated by rhinovirus infection.\textsuperscript{47} In a pilot observational study of the detection rate of human rhinovirus and \textit{C. pneumoniae} in induced sputum of COPD patients during 43 exacerbations, we found that patients treated with macrolides had a faster median recovery rate than those not treated with macrolides.\textsuperscript{48} Thus, further study is required of the effect of the anti-inflammatory
action of macrolides, with appropriate longer-term outcome measures, to check for adverse effects such as bacterial resistance.

**Prevention of COPD Exacerbations**

Any therapy that can prevent exacerbations will have important economic benefits and improve health status. As upper respiratory tract infections are common factors in causing exacerbation, influenza and pneumococcal vaccinations are recommended for all patients with substantial COPD. A study on outcome of influenza vaccination with a cohort of elderly patients with chronic lung disease found that influenza vaccination is associated with significant health benefits, with fewer out-patient visits, fewer hospitalizations, and reduced mortality. Long-term antibiotic therapy has been used in clinical practice with patients who suffer very frequent exacerbations, though there is little evidence of effectiveness.

Mucolytic agents have also been prescribed for COPD, though their use worldwide is variable, with little use in the United Kingdom and Australia and more prescriptions in Europe. A recent meta-analysis assessed the effects of oral mucolytics in COPD. A total of 23 randomized, controlled trials were identified, and the main outcome was that there was a 29% reduction in exacerbations with mucolytic therapy. The number of patients who had no exacerbations was greater in the mucolytic group and days-of-illness was lower in the mucolytic-treated group, though mucolytics had no effect on lung function. The drug that contributed most to the beneficial results in the review was N-acetylcysteine, though its mechanism of action is not entirely clear and may be a combination of mucolytic and antioxidative effects. Further large studies on the effects of mucolytics are in progress and the results will be available shortly.

In the recent Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study of long-term inhaled steroids in patients with moderate-to-severe COPD, there was a reduction in exacerbation frequency of around 25%. However, the overall exacerbation frequency was relatively low in the studied group, and this was probably due to a retrospective assessment of exacerbation. The effect of inhaled steroids was greater in patients with more impaired lung function, suggesting that this is the group to target with long-term inhaled steroid therapy. Another earlier study suggested that the severity of exacerbations may be reduced with inhaled steroid therapy. An observational study showed that exacerbations were increased following withdrawal of inhaled steroids, though that study was not placebo-controlled. Two recent studies have also shown that small reductions in exacerbations can be achieved with bronchodilator therapy, though both studies involved relatively short periods of therapy, at 12 weeks. Recently, the new long-acting anticholinergic agent tiotropium has been shown to reduce exacerbations by 24% when studied over a 1-year period, together with a reduction in hospitalizations. Longer-term studies of the effects of bronchodilators on COPD exacerbation are now required.

Exacerbation frequency increases with progressive airflow obstruction and, thus, patients with chronic respiratory failure are particularly susceptible to exacerbation. Following the early experience with domiciliary, long-term, noninvasive positive-pressure ventilation (NPPV) in patients with chest wall and neuromuscular disease, NPPV has also been evaluated in patients with hypercapnic COPD. An early observation on the effect of NPPV came from a randomized cross-over study in which NPPV given at home over a 3-month period had a significant beneficial effect on health status, measured with the St George’s Respiratory Questionnaire, though exacerbations were not measured in that study. Because health status is an important determinant of exacerbation frequency, it is possible that the improvement in health status is due to a reduction of exacerbation frequency. Two open studies have shown that NPPV in patients with hypercapnic COPD is associated with a reduction in hospitalization. Thus, larger, controlled studies that are adequately powered for study of exacerbations are now required to evaluate the effect of NPPV, together with study of the cost-effectiveness of and patient compliance with NPPV.

**Summary**

COPD exacerbations are an important cause of morbidity and mortality and have substantial economic consequences. There has been a considerable increase in understanding of the causes and nature of exacerbations and this has opened the door for novel interventions. More strategies to reduce exacerbation frequency urgently need to be developed and evaluated in large randomized, controlled trials. We will then be in a better position to significantly reduce the morbidity associated with COPD exacerbation and at last improve the quality of life of our patients with this disabling condition.

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**Wedzicha:** By eradication I mean long-term antibiotic therapy. The fact that we have not managed to do this yet means that we don’t quite know how to do it. I think the problem is that we need better antibiotics. We need more specific antibiotics against *Haemophilus influenzae*. The current antibiotics probably were not specific enough, and we also need to understand how long to administer antibiotics. We need to do a number of pilot studies and to really understand the outcomes, which would probably be exacerbation rate, airway inflammation, and FEV1 decline. The time has come to develop appropriate antibiotics to have a look at this issue.

**MacIntyre:** Is delivering antibiotics via aerosol attractive? Or does it matter?

**Wedzicha:** The aerosol route is attractive, except that, again, we need to have the right antibiotics. We will need a number of pilot studies. From first principles I would say you need to treat a patient probably for a year, or perhaps you need to treat them only...
during the winter months, because that’s when most of the problems occur. Once the microbiologists are convinced that we have the right antibiotics, then we can go forward. But it’s quite a task. I don’t think we can just jump in with any agent at present, because we could do more harm than good.

**Hill:** I’d like to follow up on the relationship between bacterial load and the frequency of exacerbations. What do you do to make sure your cultures represent airway bacterial load, as opposed to oral contamination? How accurate do you think your culture techniques are? And do you think these patients have higher bacterial loads because they have more severe disease, or do they have more severe disease because they have higher bacterial loads? In other words, you have an association; what is the causal relationship?

**Wedzicha:** We do not know whether the higher bacterial load causes the more severe disease or the more severe disease causes the higher bacterial load. The only way to work that out is to reduce the inflammation and see the effect or reduce the bacterial load and observe the result. It would be interesting to look at some interventions much more carefully; for example, comparing exacerbations treated with steroids and no steroids. If we can reduce inflammation, can we eradicate bacteria? If we eradicate bacteria, can we reduce inflammation? I think we can’t answer that.

The other question—how we obtain the bacteria samples—is easier to answer. When we did the airway epithelial cell work, we used the closed-brush technique, so the organisms were taken from the lower airways. Otherwise, we used spontaneous sputum and we now only use induced sputum if we cannot obtain spontaneous sputum, because our patients got fed up with producing induced sputum samples. There is a small group who produce induced sputum despite no spontaneous sputum. What we ask the spontaneous sputum producers to do is produce one sample that we discard, and then we take the second sample. Of course, we cannot be certain it is not coming from the nose, but we hope to have some data on that soon, as we are also now collecting upper airway samples.

**Hansen-Flaschen:** I’m sure you have separated current smokers from nonsmokers. Are there important differences in your results between current and former smokers?

**Wedzicha:** We have at every stage corrected for smoking and looked at differences in smoking habit in our cohort. The only relationship we have found with current smoking has been in differences in exacerbation frequency. The frequent exacerbators tend to be the smokers. We did, of course, correct for smoking in the FEV₁ decline relationships to exacerbation frequency data. One of the problems is that a number of our patients stopped smoking over the study period, which rather muddles the whole analysis. I think to get a good analysis of smoking and exacerbations, you need a much larger study. But certainly, the smokers seemed to be getting the longer exacerbations.

**Hansen-Flaschen:** Do your patients die during exacerbations? Is that the pathway to death when someone dies of lung disease with COPD?

**Wedzicha:** The patients with severe COPD do die of respiratory failure. The mortality rate is currently around 5%, which is actually rather low because we see patients early, and I think that is one of the reasons we prevent hospitalization and mortality. However, patients with moderate COPD die from cardiovascular conditions such as stroke and ischemic heart disease. So I think the relationship between COPD and cardiovascular disease is important; these people have high fibrinogen levels.

**Make:** You defined exacerbations and said 2 or more major symptoms or 1 major symptom plus 1 minor symptom. Is there a difference between these 2 categorizations of exacerbation?

**Wedzicha:** Good question. We looked at this point right at the very beginning and showed that whether you had 2 symptoms—two of them major, or 1 major and 1 minor—there was little difference. It would be very useful to do that analysis again to see if there is a difference. It is likely that we will find that exacerbations with 2 major symptoms are much more severe over time, because there would be more sputum production. Thank you for the suggestion, Barry.

**Fahy:** What is the patient-education take-home message from this?

**Wedzicha:** The patient-education take-home message is, “Learn how to detect your exacerbations.” Some patients are not very good at detecting their exacerbations and some patients are poor reporters of exacerbations. The second message is, “Get treatment early and try to prevent nonrecovery and disease progression.”

**Benditt:** Your point about the one-and-a-half day exacerbation prodrome is really important, because there’s been a lot of talk about trying to prevent rhinovirus infections with an agent that’s now available for that. It would seem to me it’d be much more effective to work on development of vaccines for prevention of viral infection. Unfortunately, it doesn’t sound like influenza vaccination is really that helpful, because it’s such a small percentage.

**Wedzicha:** I think there would be more influenza infection if they were not vaccinated. There is good data.
from Nichol et al1 that influenza vaccination works. The problem with rhinovirus vaccines is that there’s about 100 different types of rhinovirus. Within one study we had 10 different types of rhinovirus. So I think vaccination for rhinovirus is not possible in the near future. However, if an anti-rhinoviral agent were available, you could treat patients between November and April, since that’s the rhinovirus season, and you could prevent rhinovirus infections. That is probably the way you will have to use any future therapies. Patients who are very good at recognizing their exacerbations might even be able to take the drug acutely. But I think that’s difficult.

The other important virus is RSV [respiratory syncytial virus]. We have found substantial RSV in the stable state. We are currently analyzing RSV in our whole cohort. RSV would be easier to control and there are some quite good therapies.

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Make: Can I follow up on Bonnie Fahy’s question about take-home messages for patients and educating them on how to recognize their symptoms? I think we’re all familiar with the multiple symptoms that you described as being key to defining exacerbations, but we don’t put any timeframe on that for our patients. You found a one-and-a-half day prodrome, but patients will have these symptoms periodically for a couple hours or half a day, probably very regularly. Is there any timeframe we should tell our patients about? For example, if they have these symptoms for more than a day, should they report to us?

Wedzicha: We looked at how many 1-symptom and 2-symptom episodes for 1 day, and there are a lot of isolated symptoms, so we tell patients that if they have 2 days of symptoms, they should call us. Ideally, for our study, we like to see them. When we did our first [study], we told the patients to call us at the onset of anything, and then we had to discard episodes that were not exacerbations, because we were so keen to detect viruses. You have to sample viruses very early in an exacerbation if you want to detect them. Patients are now told to call us after 2 days of symptoms, and there is a telephone help line. We work in a very poor socio-economic area of London, and patients still do not use our exacerbation help line as much as we would like.

Make: What’s the usefulness in patients who present with symptoms of exacerbations for measuring anything? In other words, do you just treat your patients when you’re not doing a study?

Wedzicha: Clinical diagnosis.

Make: Let me tell you why I ask; it’s not to make a diagnosis but to help assist with the type of therapy. For example, do you do pulse oximetry and measure FEV1?

Wedzicha: If we are worried that the patient may have a severe exacerbation and be in respiratory failure in our hospital, we measure blood gases via the ear lobe. We have an instant service, so we measure blood gases if we think there may be a problem or the patient is in respiratory failure. It is generally not worth measuring spirometry at exacerbation, as the changes are too small. If you are doing a study and you need to prove that the patient had an exacerbation, the best test is plasma fibrinogen, because that almost always increases with exacerbations.