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Exacerbations*

Etiology and Pathophysiologic Mechanisms

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Some patients with COPD are prone to frequent exacerbations, which are an important determinant of health status. Such patients have elevated airway cytokine levels, suggesting the presence of increased inflammation that may increase their susceptibility to exacerbation. The inflammatory response during a COPD exacerbation is variable, but increases in interleukin-6 levels during the exacerbation are related to the presence of a common cold. Rhinovirus infection is the most important etiologic factor in COPD exacerbations and is an important target for preventive therapy. The reduction of COPD exacerbations will have an important impact on the considerable morbidity and mortality associated with COPD.
(CHEST 2002; 121:136S–141S)

Key words: bacterial infection; COPD; endothelin-1; epidemiology; exacerbations; interleukin-6; interleukin-8; pollution; rhinovirus; virus infection

Abbreviations: ICAM = intercellular adhesion molecule; IL = interleukin

There has been considerable interest in the causes and mechanisms of exacerbations of COPD because such exacerbations are an important cause of the considerable morbidity and mortality found in patients with COPD.[1] COPD exacerbations increase with increasing disease severity, and some patients are prone to frequent exacerbations, which constitutes an important cause of hospital admission and readmission, and such exacerbations may have a considerable impact on quality of life and the activities of daily living.[2] COPD exacerbations also are associated with considerable physiologic deterioration and increased airway inflammatory changes[3] that are caused by various factors such as viruses, bacteria, and possibly common pollutants (Fig 1). COPD exacerbations are more common in the winter months, and there may be important interactions between cold temperatures and exacerbations caused by viruses or pollutants.[4]

Earlier descriptions of COPD exacerbations had concentrated mainly on studies of hospital admissions, although most exacerbations are treated in the community and are not associated with hospital admission. A cohort of patients with moderate-to-severe COPD was observed in the East London COPD Study by means of daily diary cards and peak flow readings, and they were asked to report exacerbations as soon as possible after symptomatic onset.[2] The diagnosis of COPD exacerbation was based on criteria modified from those described by Anthonisen and colleagues,[5] which require two symptoms for diagnosis, one of which must be a major symptom such as increased dyspnea, sputum volume, or sputum purulence. Minor exacerbation symptoms included cough, wheeze, sore throat, nasal discharge, or fever. The study found that about 50% of exacerbations went unreported to the research team, despite considerable encouragement, and were diagnosed only from diary cards, although there were no differences in major symptoms or physiologic parameters between reported and unreported exacerbations.[2] Patients with COPD are accustomed to frequent symptom changes and, thus, may tend to under-report exacerbations to physicians. These patients have high levels of anxiety and depression and may accept their situation.[6,7] The tendency of patients to under-report exacerbations may explain the total rate of exacerbations (2.7 exacerbations per patient per year), which is higher than that previously reported by Anthonisen and coworkers[5] (1.1 exacerbations per patient per year). In the latter study, however, exacerbations were unreported and were diagnosed from patients' recall of symptoms.

Using the median number of exacerbations as a cutoff point, COPD patients in the East London Study were classified as frequent and infrequent exacerbators. Quality-of-life scores, which were measured using a validated disease-specific scale (*ie*, the St. George's Respiratory Questionnaire), were significantly worse in all three component scores (*ie*, symptoms, activities, and impacts) among frequent exacerbators compared to infrequent exacerbators. This suggests that exacerbation frequency is an important determinant of health status among patients with COPD and is thus one of the important outcome measures of this disease. Factors that are predictive of frequent exacerbations included daily cough and sputum, and frequent exacerbations in the previous year. A previous study[8] of acute infective exacerbations of chronic bronchitis found that one of the factors predicting exacerbation was also the number of exacerbations experienced in the previous year. This study, however, was limited to patients with exacerbations who were presenting with purulent sputum, and no physiologic data were available from the study.

In a further prospective analysis[9] of 504 exacerbations in which daily monitoring was performed, there was some deterioration in symptoms reported, although there were no significant peak flow changes. Falls in peak flow and FEV_1 during exacerbations were generally small and were not useful in predicting exacerbations, but larger falls in peak flow were associated with symptoms of dyspnea and the presence of colds, and were related to longer recovery times from exacerbations. Symptoms of dyspnea, common colds, sore throat, and cough increased significantly during the prodromal phase, and this suggests that respiratory viruses may have early effects during exacerbations. The median time to recovery of peak flow was 6 days, and the median time to recovery from symptoms was 7 days. At 35
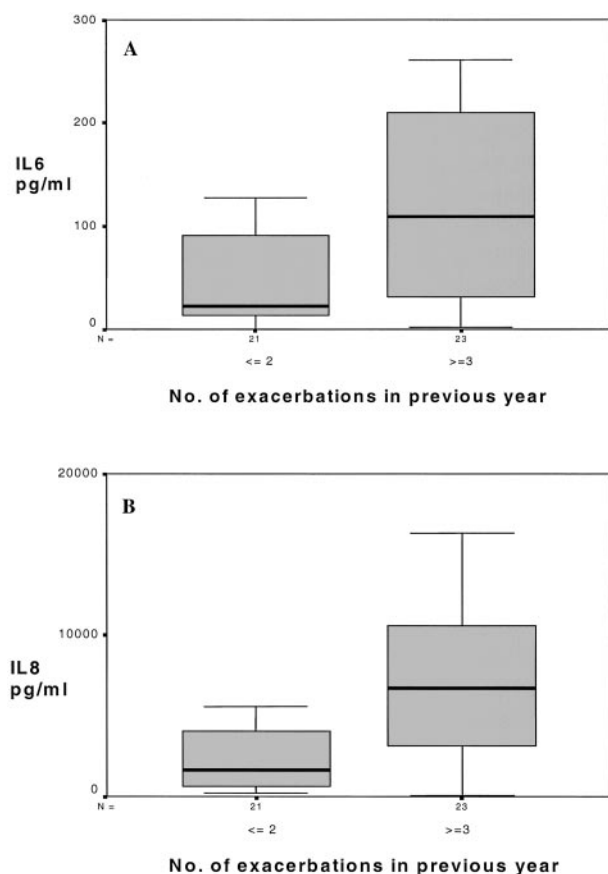
FIGURE 1. *Top*, *A*: induced sputum levels of IL-6 in patients who are categorized as frequent exacerbators (*ie*, patients who have experienced three or more exacerbations in the previous year) and in those patients who are categorized as infrequent exacerbators (*ie*, patients who have experienced two or fewer exacerbations in the previous year). *Bottom*, *B*: induced sputum levels of IL-8 in patients with frequent exacerbations and infrequent exacerbations. Data are expressed as medians (interquartile range). Reproduced with permission from Bhowmik et al.[3]

days, peak flow had returned to normal in only 75% of patients who had experienced exacerbations, while at 91 days, 7.1% of patients who had experienced exacerbations had not returned to baseline levels of lung function. Recovery was longer in the presence of increased dyspnea or symptoms of a common cold at exacerbation. The changes observed in lung function during COPD exacerbations were smaller than those observed during asthmatic exacerbations, although the average duration of an asthmatic exacerbation was longer (9.6 days).[10,11]

The reasons for the incomplete recovery of symptoms and lung function are not clear but may involve inadequate treatment or the persistence of the causative agent. Incomplete physiologic recovery after an exacerbation could contribute to the decline in lung function with time among patients with COPD. However, to date there has been no evidence reported that patients with incomplete recovery from their exacerbations have a greater decline in lung function, and further studies on the natural history of COPD exacerbations are required. The association of the

symptoms of increased dyspnea and the common cold during exacerbation with a prolonged recovery suggests that viral infections may lead to more prolonged exacerbations. Because colds are associated with longer exacerbations, COPD patients who develop a cold may be prone to more severe exacerbations and should be considered for early therapy, at the onset of symptoms.

Airway Inflammation During Exacerbation

Although it often has been assumed that exacerbations are associated with increased airway inflammation, there has been little information available on the nature of inflammatory markers, especially when they have been studied close to the occurrence of an exacerbation, because performing bronchial biopsies during an exacerbation is difficult in patients with moderate-to-severe COPD. The relationship of any airway inflammatory changes to symptoms and physiologic changes during exacerbations of COPD is also an important factor to consider.

In one study,[12] in which biopsies were performed during exacerbations in patients with chronic bronchitis, increased airway eosinophilia was found, although the patients studied had only mild COPD. With exacerbations, there were more modest increases observed in neutrophils, T lymphocytes (CD3+), and tumor necrosis factor-α-positive cells, while there were no changes in the numbers of CD4+ or CD8+ T cells, macrophages, or mast cells. However, the technique of sputum induction allows the study of these patients during exacerbations, and it has been shown that it is safe and well-tolerated in COPD patients.[13] The levels of inflammatory cytokines have been shown to be elevated in induced sputum from COPD patients when their condition is stable, although changes during exacerbations had not been studied previously.[14]

In a prospectively followed cohort of patients from the East London COPD Study,[3] the presence of inflammatory markers in induced sputum was related to symptoms and physiologic parameters both at baseline and during exacerbations. There was a relationship between exacerbation frequency and the level of sputum cytokines, in that there were increased levels of interleukin (IL)-6 and IL-8 found in the sputum of patients who had been stable at baseline who experienced frequent exacerbations compared to those who experienced infrequent exacerbations (Fig 1), although there was no relationship between the level of cytokines and baseline lung function. Sputum cell counts were not higher at baseline in patients with more frequent exacerbations, suggesting that the increased cytokine production came from the bronchial epithelium in patients with COPD. 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,[15] and thus, repeated viral infection may lead to the up-regulation of cytokine airway expression.

During exacerbation, increases were found in the level of IL-6 in induced sputum, and the levels of IL-6 were higher when exacerbations were associated with symptoms

of the common cold (Fig 2). Experimental rhinovirus infection has been shown to increase sputum IL-6 levels in healthy subjects and asthmatic patients.[16–18] Rising cell counts and increasing levels of IL-8, however, were more variable with exacerbation and did not reach statistical significance, suggesting marked heterogeneity in the degree of the inflammatory response during an exacerbation. IL-8 levels during an exacerbation were related to sputum neutrophil and total cell counts, indicating that neutrophil recruitment is the major source of airway IL-8 during an exacerbation. Airway IL-8 level has been shown to increase with the presence of experimental rhinovirus infection in healthy and asthmatic patients in some studies,[17] but not in others.[18] However, COPD patients already have up-regulated airway IL-8 expression when they are stable due to their high sputum neutrophil load,[14] and further increases in IL-8 levels would be unlikely. COPD exacerbations are associated with less pronounced airway inflammatory responses than are asthmatic exacerbations,[19] and this may explain the relatively reduced response to corticosteroid therapy seen during exacerbations in COPD patients, compared to responses during exacerbations in asthma patients.[20–26]

In the study by Bhowmik and colleagues,[3] there was no increase seen in the eosinophil count during exacerbations, although the patients in that study were sampled early during the exacerbation, with onset of symptoms. Compared to the study by Saetta and colleagues,[12] in which patients had mild COPD, the patients had more severe and irreversible airflow obstruction (FEV_1, 39% of predicted). It is possible, therefore, that the inflammatory response during an exacerbation is different in nature in patients with moderate-to-severe COPD than in those with milder cases of COPD.

Patients were followed-up with daily diary cards in the study by Bhowmik et al[3] and, thus, the inflammatory markers could be related to exacerbation recovery. There was no relationship between the degree of inflammatory cell response with exacerbation and the duration of symptoms and the number of lung function changes. The levels of markers in induced sputum that were obtained 3 to 6 weeks after exacerbations showed no relationship to exacerbation changes. Thus, levels of induced sputum markers during an exacerbation do not predict the subsequent course of the exacerbation and will not be useful in the prediction of exacerbation severity.

ETIOLOGY OF COPD EXACERBATION

COPD exacerbations have been associated with a number of etiologic factors, including respiratory infection and pollution episodes (Table 1).

Viral Infections

Viral infections are important triggers for COPD exacerbations, which are frequently triggered by upper respiratory tract infections. These infections are more common in the winter months when there are more respiratory viral infections present in the community. Patients also may be more prone to exacerbations in the winter months as lung function in COPD patients has shown small but significant falls with reduction in outdoor temperature during the winter months.[4]

Studies[27] of childhood asthma have shown that viruses, especially rhinovirus (the cause of the common cold) can be detected by polymerase chain reaction from a large number of these exacerbations. Rhinovirus has not hitherto been considered to be of much significance during exacerbations of COPD. In a study of 44 patients with chronic bronchitis performed over 2 years, Scott and colleagues[28] found rhinovirus in 13 of 87 exacerbations (14.9%) of chronic bronchitis. In a more detailed study of 25 chronic bronchitis patients who experienced 116 exacerbations over > 4 years, Gump et al[29] found that only 3.4% of exacerbations could be attributed to rhinoviruses. In a more recent study[30] of 35 episodes of COPD exacerbation using serologic methods and nasal samples
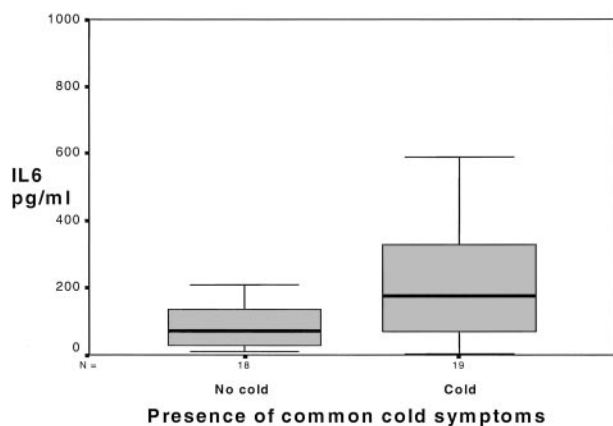

FIGURE 2. Induced sputum IL-6 levels in the absence and presence of a natural cold. Data are expressed as medians (interquartile range). Reproduced with permission from Bhowmik et al.[3]

Table 1—Causes of COPD Exacerbations

Viruses
Rhinovirus (common cold)
Influenza
Parainfluenza
Coronavirus
Adenovirus
Respiratory syncytial virus
C pneumoniae
Bacteria
H influenzae
S pneumoniae
M catarrhalis
Staphylococcus aureus
P aeruginosa
Common pollutants
Nitrogen dioxide
Particulates
Sulphur dioxide
Ozone

for viral culture, little evidence was found for a rhinovirus etiology of COPD exacerbation.

Two recent studies[31,32] reported that at least one third of COPD exacerbations were associated with viral infections, the majority being due to rhinovirus. Viral exacerbations were associated with symptomatic colds and prolonged recovery.[9] However, Seemungal and colleagues[32] showed that rhinovirus can be recovered from induced sputum more frequently than from nasal aspirates during an exacerbation, suggesting that wild-type rhinovirus can infect the lower airway and contribute to inflammatory changes during an exacerbation. They also found that patients with exacerbations that were associated with the presence of rhinovirus in induced sputum had larger increases in airway IL-6 levels,[32] suggesting that viruses increase the severity of airway inflammation during the 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.[9,32] Other viruses may trigger COPD exacerbations, although coronavirus was associated with only a small proportion of asthmatic exacerbations and is unlikely to play a major role in COPD.[29,33]

There are a number of mechanisms that may be involved in the association between viruses and exacerbations. The major group of rhinovirus (accounting for 90% of total rhinovirus types) attaches to the airway epithelium through the intercellular adhesion molecule (ICAM)-1, inducing ICAM-1 expression, thereby promoting inflammatory cell recruitment and activation, as is seen in exacerbations.[34] The minor rhinovirus group uses members of the LDL-receptor family as cell surface receptors, although ICAM-1 surface expression also may be up-regulated.[34] There is some evidence for the up-regulation of ICAM-1 in the bronchial mucosa of patients with chronic bronchitis,[35] and ICAM-1 may represent an important therapeutic target in COPD exacerbations that are associated with rhinoviruses.

Viral infections have been associated with increased oxidant stress, which is increased during COPD exacerbations.[36] Rhinovirus infection of human respiratory epithelial cells increases the production of reactive oxygen species and stimulates the activation of nuclear factor-κB, which is important in the regulation of the IL-8 gene.[37] In patients with experimental rhinovirus infections, nasal IL-8 levels have been related to common cold symptoms.[38] Viral infections also can induce the expression of stress-response genes (eg, heme-oxygenase-1) and genes encoding antioxidant enzymes (eg, glutathione peroxidase and Mn-superoxide dismutase),[39] and these may be important in potentiating the effects of the virally mediated inflammation during a COPD exacerbation. We also have shown that exacerbations are associated with increased airway and systemic endothelin-1 levels.[40] Endothelin-1 is an important bronchoconstrictor peptide that has been found to be proinflammatory and also has been implicated in the pathogenesis of virally mediated inflammation.[41] Sputum endothelin-1 levels increase during COPD exacerbations and are related to sputum IL-6 levels. Further work with specific endothelin receptor antagonists may provide a new therapeutic option for inflammation associated with COPD exacerbations.

Associations have been described between chronic bronchitis and death from cardiovascular disease.[42] Plasma fibrinogen is an independent risk factor for cardiovascular disease,[43] and we have shown that plasma fibrinogen levels are increased in COPD patients, thus making them susceptible to ischemic events.[44] During an exacerbation, we found increased levels of plasma fibrinogen and IL-6, which stimulate the production of fibrinogen, and these levels were higher in the presence of viral infections.[44] Epidemiologic studies have suggested that infections, especially those of the respiratory tract, may be involved in the onset of myocardial infarction and stroke,[45] and patients who have frequent exacerbations with their recurrent infections may be particularly susceptible to cardiovascular disease.

Bacterial Colonization

Airway bacterial colonization has been found in approximately 30% of COPD patients and has been shown to be related to the degree of airflow obstruction and current cigarette smoking status.[46] Although bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* have been associated with COPD exacerbations, some studies[47,48] have shown increasing bacterial counts during exacerbation, while others have not confirmed this. Soler and colleagues[49] showed that the presence of potentially pathogenic organisms in BAL fluid from COPD patients obtained during bronchoscopy was associated with a greater degree of neutrophilia and higher tumor necrosis factor-α levels. In a larger study, Hill and colleagues[50] showed that the airway bacterial load was related to the presence of inflammatory markers. They also found that the type of bacterial species was related to the degree of inflammation, with *Pseudomonas aeruginosa* colonization showing greater myeloperoxidase activity (an indirect measure of neutrophil activation). Exacerbations associated with purulent sputum were more likely to produce positive bacterial cultures than are exacerbations in which the sputum production was mucoid.[51] Sethi and colleagues[52] have shown that exacerbations associated with *H influenzae* and *Moraxella catarrhalis* are associated with significantly higher levels of airway inflammatory markers and neutrophil elastase, compared to pathogen-negative exacerbations.

Thus, bacterial colonization in patients with COPD may be an important determinant of airway inflammation, and further long-term studies are required to discern whether bacterial colonization predisposes patients to the decline in lung function that is characteristic of COPD. However, it is also possible that there may be interactions between viral and bacterial infections during COPD exacerbations. Other organisms such as *Chlamydia pneumoniae*, which have been associated with asthmatic exacerbation, also may play a role in COPD exacerbation. Further evaluation is required.

Pollution

There has been considerable interest in the effects of air pollution on COPD exacerbations, especially with respect to the effects of common pollutants on hospital admissions. COPD patients have been found to have increased numbers of hospital admissions, suggesting increased numbers of exacerbations when increasing environmental pollution occurs. During the December 1991 pollution episode in the United Kingdom, the COPD mortality rate increased together with an increase in hospital admissions among elderly COPD patients.[53] Data from a study of air pollution in six European cities (Air Pollution and Health, a European Approach project) showed that the relative risks for COPD hospital admissions due to increases of 50 $\mu g/m^3$ in the daily mean level of pollutants (with lags from 1 to 3 days) were 1.02 for SO_2, NO_2, and total suspendable particles, and 1.04 for ozone.[54] An analysis of data from Birmingham, AL,[55] also showed that the inhalation of particles carried a relative risk of 1.27 for hospital admissions for COPD. Generally, the most convincing relationship for hospital admission due to COPD has been with the level of particulate pollution. Studies also have shown relationships with NO_2 exposure, and a study from Australia has suggested an increase of 4.6% in COPD hospital admissions with NO_2 exposure.[56]

Although there is considerable epidemiologic data that increased pollutants are associated with COPD hospital admissions, the mechanisms involved are largely unknown. As COPD exacerbations are closely linked to respiratory infections, the hypothesis that pollutants can increase susceptibility to viral infections has been proposed. One study[57] investigated the effect of NO_2 exposure in a controlled chamber on the susceptibility to infection with influenza and found some small increases in effect with the combination of virus and pollutant. Another study[58] investigated the effects of personal exposure to NO_2 on the risk of airflow obstruction in asthmatic children with respiratory infections. This study suggested that with higher personal pollutant exposure, there was a greater risk of an asthmatic exacerbation following a respiratory infection. Thus, similar mechanisms may be operating in patients with COPD, and further studies are required on the association of pollution and infection.

Conclusion

This article has described some important characteristics of COPD exacerbations. Some patients with COPD are prone to frequent exacerbations, which are an important determinant of health status. These patients have higher airway cytokine levels, suggesting increased airway inflammation, which could increase patients' susceptibility to exacerbations. The inflammatory response during a COPD exacerbation is variable, but rising levels of IL-6 during exacerbations are related to the presence of a common cold. Rhinovirus infection is the most important etiologic factor in COPD exacerbations and is an important target for preventive therapy. A reduction in COPD exacerbations will have an important impact on the considerable morbidity and mortality associated with COPD.

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