Granulocyte Inflammatory Markers and Airway Infection during Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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There is increasing evidence that chronic obstructive pulmonary disease (COPD) is associated with chronic inflammation in the airways and lung parenchyma; however, little is known about the inflammatory response during acute COPD exacerbation. The objectives of this study were (1) to determine if inflammatory markers associated with neutrophilic inflammation and activation increase at times of acute COPD exacerbation relative to the clinically stable state, and (2) to determine whether the presence of acute bacterial or viral infection at the time of COPD exacerbation could be correlated with increases in sputum markers of inflammation. Induced sputum was collected from patients with COPD when they were clinically stable, during the time of an acute exacerbation, and 1 mo later. Sputum was analyzed at each time point for soluble markers associated with neutrophilic inflammation; myeloperoxidase (MPO), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8). Serologic assays on acute and convalescent sera were performed for respiratory viruses, and induced sputum was also subject to quantitative bacterial cultures, viral cultures, and polymerase chain reaction (PCR) for detection of respiratory viruses. Fourteen of the 50 patients enrolled in the study met predetermined criteria for an acute COPD exacerbation over the 15-mo study period. TNF-α and IL-8 were significantly elevated in the sputum of patients during acute COPD exacerbation compared with when they were clinically stable (p = 0.01 and p = 0.05, respectively). Concentrations of these cytokines declined significantly 1 mo after the exacerbation. Three of 14 patients (21%) had confirmed bacterial or viral respiratory tract infections. Patients with documented infection did not demonstrate greater increases in sputum levels of inflammatory cytokines during exacerbations compared with patients without demonstrable infection. We conclude that markers of airway neutrophilic inflammation increase at the time of acute COPD exacerbation and then decline 1 mo later, and that this acute inflammatory response appears to occur independently of a demonstrable viral or bacterial airway infection.

There is increasing evidence that chronic obstructive pulmonary disease (COPD) is associated with chronic inflammation in the airways and lung parenchyma (1, 2). Patients with clinically stable COPD are known to have increased numbers of neutrophils and macrophages in their sputum and bronchoalveolar lavage fluid (BALF) relative to normal subjects (3). Studies of induced sputum from stable COPD patients have revealed elevated levels of the granulocyte activation markers myeloperoxidase (MPO) and human neutrophil lipocalin (HNL) (4). The neutrophil chemoattractants interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) are also elevated in stable COPD patients relative to normal control subjects, suggesting that neutrophil recruitment and activation may play a role in the pathogenesis of chronic airflow obstruction (5).

Patients with COPD are prone to periodic exacerbations of their illness with worsening of their respiratory symptoms. Airway inflammation is presumed to play an important role in the pathogenesis of worsening of airflow obstruction seen during acute exacerbations of COPD (6). Studies of patients with mild COPD who were examined during an exacerbation of their disease showed increased numbers of eosinophils, neutrophils, CD-3 lymphocytes, and TNF-α-positive cells in bronchial biopsies compared with other COPD patients examined under conditions of clinical stability (6). Similarly, other investigators have shown that patients with COPD who experience frequent exacerbations (≥ 3 exacerbations/year) have higher concentrations of IL-6 and IL-8 in induced sputum compared with patients who experience fewer exacerbations (7).

Although these studies suggest that patients with COPD exacerbation show evidence of increased inflammatory activity relative to control subjects, there are no longitudinal studies that have compared concentrations of inflammatory markers in individual patients before, during, and after an acute COPD exacerbation.

The most common triggers of acute COPD exacerbation are thought to be bacterial and viral respiratory tract infections (8). COPD exacerbations have been associated with acute respiratory tract infections with rhinovirus (9), respiratory syncytial virus (RSV) (10), and influenza virus (10), as well as with endobronchial bacterial infections with gram-positive and gram-negative bacteria (11). However, definite determination of an infectious cause of COPD exacerbation can be difficult, and it is not known whether a relationship exists between acute respiratory tract infections and airway inflammation (8). Acute viral infections have been shown to increase airway responsiveness, and viral-induced airway epithelial damage is known to result in airway inflammation and edema (12). Similarly, bacterial airway infections are associated with purulent sputum and sputum neutrophilia (13). Theoretically, one might therefore expect that exacerbations of COPD due to viral or bacterial infection would be associated with increased airway inflammation and elevated levels of airway inflammatory cytokines.

The objectives of this study were thus twofold. The first objective was to determine if inflammatory markers associated with neutrophilic inflammation and activation increase at times of acute COPD exacerbation relative to the clinically stable state. The second objective was to determine whether evidence of acute bacterial or viral infection could be found at the time of COPD exacerbation, and whether the presence of documented infection could be correlated with increases in sputum markers of inflammation.
METHODS

Study Subjects

Fifty patients with clinically stable COPD were recruited over a 6-mo period from the outpatient clinics and the pulmonary function laboratories of the Ottawa Hospital. All of the patients met British and American Thoracic Society criteria for the diagnosis of COPD, and all had evidence of chronic, slowly progressive airflow obstruction which was largely fixed, without significant reversibility. In order to enter the study, the patient had to have satisfied the following inclusion criteria: (1) a previous clinical diagnosis of COPD, chronic bronchitis, or emphysema; (2) age > 40 yr; (3) a previous history of at least 10 pack-years of smoking; and (4) stable airflow limitation with FEV1 < 70% predicted. FEV1/forced vital capacity ratio < 0.7, and salbutamol reversibility of < 15% or 200 ml. Exclusion criteria included: (1) a history of asthma or atopy; (2) current smoking or history of having smoked within 6 mo of assessment; (3) use of chronic oral or parenteral steroids; (4) history of bronchiectasis, lung cancer, or congestive heart failure. Current smokers were excluded because previous studies have suggested that cigarette smoking induces the production of IL-8 in the airways (5).

Patients were recruited when they were clinically stable, and subjects who had suffered a respiratory tract infection or exacerbation of airways disease within the previous 4 wk were excluded from the study. On the day of recruitment into the study the patient’s baseline clinical and demographic information was collected and the patient underwent pre- and postbronchodilator spirometry followed by sputum induction. All subjects gave informed written consent and the study was approved by the ethics committee of the Ottawa Hospital.

Exacerbations

Patients were followed for 9 to 15 mo after recruitment into the study. Each enrolled patient received regular phone calls and written notices instructing the patient to report to one of the two study pulmonary physicians when he or she noticed a deterioration in symptoms. Exacerbations of COPD were diagnosed according to criteria from Anthonsen and colleagues (14). The patient had to have experienced any two of the three major symptoms—increase in dyspnea, sputum purulence, and increased sputum volume—in order to be classified as having a COPD exacerbation. The diagnosis of exacerbation was confirmed in each case by a pulmonary physician. Spirometry was performed on the day of the exacerbation visit, a chest radiograph was done, and induced sputum samples and blood samples were taken. After sputum and blood sampling the patients were treated with either antibiotics or oral corticosteroids or both, for 10 to 14 d. Patients were then reassessed 1 mo after the date of the exacerbation. Spirometry was repeated, blood samples were taken for convalescent viral serologies, and induced sputum samples were again taken at this 1 mo visit.

Sputum Induction and Processing

Spirometry was recorded before and 15 min after inhalation of salbutamol 200 μg by means of a metered-dose inhaler. Sputum induction was performed according to previously described protocols (15). Subjects inhaled 0.9% saline at room temperature, nebulized using an ultrasonic nebulizer (DeVilbiss Ultraneb 99; DeVilbiss, Heston, UK) at maximal output (6 ml/min) for 4 min. The subject was then instructed to blow his nose and drink water and then cough sputum into a polypropylene pot. Sputum induction was stopped once 2 ml of sputum was collected. Saliva produced during the procedure was discarded. If an adequate volume of sputum was not obtained, and providing the FEV1 had not fallen by > 10% from baseline levels, then the sputum induction procedure was repeated with 3.0% saline for 4 min and finally with 5.0% saline for 4 min.

After the sputum induction, the sputum samples were refrigerated at 4°C for not more than 2 h and were then processed for Gram staining and quantitative bacterial and viral cultures. Adequacy of the sputum sample was established on initial Gram staining of the sputum. Only adequate samples containing > 25 squamous epithelial cells per low power field and > 25 leukocytes per high-power field were accepted for processing and determination of cytokine levels. For those sputum specimens that were inadequate, the sputum induction process was repeated until an adequate lower respiratory sample was obtained. After viral and bacterial cultures were performed, the remainder of the sputum was stored at −80°C until further assay for cell activation markers.

The sputum was thawed at a later date at 4°C. The sol phase was obtained by first subjecting the sample to high-speed centrifugation at 10,000 rpm for 60 min at 4°C. The entire sample was then ultracentrifuged at 60,000 g for 90 min at 4°C. This was aliquoted and the supernatant was stored at −80°C for subsequent assay for the cytokines TNF-α, IL-8, and IL-1β. The pellet was also stored frozen at −80°C for subsequent polymerase chain reaction (PCR) measurements for detection of virus. All specimens were coded and labeled by the research assistant so that the investigators performing the cytokine measurements and the PCR viral assays remained blinded to the actual sequence order of the specimens.

Cytokine Assays

IL-8 and TNF-α were measured in the supernatant samples using a quantitative sandwich immunoassay (R&D Systems, Minneapolis, MN). The lower limit of quantification for these assays was 31.2 pg/ml and 15.6 pg/ml, respectively. MPO concentrations were similarly determined by a commercially available ELISA (OXIS International, Inc., Portland, OR); the lower limit of quantification for this assay was 1.6 ng/ml.

The reproducibility of these assays was confirmed by performing repeated measurements on successive days. The intraassay correlation coefficient (R) for MPO and TNF-α measurements was 0.96 and 0.99 respectively. Samples spiked with pure compound which were then ultracentrifuged and assayed resulted in greater than 85% recovery of the three cytokines from the sol phase. The investigators performing the cytokine assays were kept blinded to the sequence order of the sputum specimens.

Detection of Infection

Viral cultures. Viral cultures were taken from freshly induced sputum samples obtained on the day of the patient’s baseline visit, exacerbation visit, and convalescent visit 1 mo later. Specimens were inoculated into human fetal lung with serum-free medium, and the virus was allowed to adsorb to the cells for 1 h. After three 2-h washes, the monolayers were fixed and stained with methylene blue. The monolayer cultures were examined for the presence of cytopathic effect (CPE) and, if CPE was not observed, the cultures were further incubated for 3 d. If CPE was noted, the monolayer cultures were examined daily for the appearance of CPE. The appearance of CPE was considered evidence of viral infection.

Viral serology. Serum was sampled on the day of exacerbation, and convalescent titers were evaluated 1 mo later. Serologic evidence of RSV, parainfluenza viruses, influenza A and B viruses [FluA and FluB], rhinovirus, and adenovirus; Baxter Healthcare Corp., Issaquah, WA).

Viral detection. Viral detection was performed by performing a battery of PCR viral screens for adenovirus, RSV, parainfluenza 1, 2, and 3, influenza A and B, parainfluenza virus 1, 2, and 3, adenovirus, rhinovirus, and subtypes A and B (nose washes, nasopharyngeal swabs, throat swabs, nasal swabs) (17, 18). Primers for adenovirus, RSV, FluA and FluB were chosen based on their previous use for detection of viruses in respiratory specimens (nasal washes, nasopharyngeal swabs, throat swabs, nasal swabs) (17, 18). FluA primers will amplify products from both H1 and H3 subtypes; RSV primers amplify from both RSV-A and RSV-B serotypes; the adenovirus primers amplify from adenovirus types 1 to 7. The

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primers for rhinovirus were selected after trial of several primer pairs suggested for use in a nested PCR (19). The two primers used in this study worked consistently on viruses from the two major groups of human rhinoviruses (HRV) (Wright KE, Sattar SA, Diaz-Mitoma F, Dales S, Dimock K, unpublished results).

RT was carried out at 37 °C overnight in the buffer provided by the manufacturer (Roche, Basel, Switzerland), with 20 mM dithiothreitol (DTT), 2 mM deoxyribonucleoside triphosphates (dNTPs), 35 U of RNAGuard (Pharmacia, Prapack, NJ), and 100 ng each of primers for HRV, FluA and FluB, and 50 units of Expand RT (Roche). For samples from eight patients, primers for RSV were also included.

All PCR reactions were carried out using buffer provided by the manufacturer (MBI Fermentas, Burlington, ON, Canada), 1.5 mM MgCl₂, 0.2 mM dNTPs, 100 ng of each relevant primer, and 2 U of Taq DNA polymerase. For detection of adenovirus, 15 μl of precipitated nucleic acid was added to 80 μl of a PCR mix containing Ad-specific primers (ADHEX3, ADHEX5). Samples from five patients were examined for HRV, and FluA and FluB only, whereas samples from nine patients were examined for the same three viruses plus RSV. For the first set of samples, complementary DNA (cDNA) was used in a multiplex PCR containing primers for HRV, FluA, and FluB only. For the second set of specimens, half of the cDNA was used in a PCR reaction containing primers for HRV and RSV, the other half in a reaction with primers for FluA and FluB. A negative control (PCR reagents with no DNA) was included with each set of reactions. Positive controls for RT were run with acute COPD exacerbation. The mean age of the 14 subjects who experienced exacerbations was 71.6 ± 7.7 yr, and 21% of the patients were female. The mean baseline FEV₁ (± SD) of the enrolled patients was 0.95 ± 0.31 L (39% of predicted).

Fourteen of the 50 patients enrolled in the study met predetermined criteria for an acute COPD exacerbation over the 15-mo study period. The mean time to exacerbation from entry into the study was 121 ± 113 d (range 7 to 358 d). Ten subjects (71%) presented with symptoms of increased sputum volume, sputum purulence, and increased dyspnea, and the remaining four patients met 2 of 3 clinical criteria for acute COPD exacerbation. The mean age of the 14 subjects who experienced exacerbations was 71.6 ± 7.7 yr, and 21% of the patients were female. The mean baseline FEV₁ of the patients who experienced exacerbation was 0.89 ± 0.24 L. The demographic characteristics of all the enrolled subjects, and of those who experienced an exacerbation, are shown in Table 1.

### Spirometric and Radiographic Results
Although there was an overall trend toward a decline in lung function during exacerbations, the declines in airflow were not statistically significant. The mean FEV₁ declined slightly from 0.89 ± 0.24 L at baseline to 0.85 ± 0.26 L on the day of exacerbation (p = 0.26). The mean FEV₁ improved slightly 1 mo after exacerbation to 0.92 ± 0.30 L (p = 0.15). Chest radiographs taken at the time of exacerbation did not reveal pneumonia or pulmonary edema in any of the 14 patients who presented with acute COPD exacerbation.

### TNF-α Concentrations
TNF-α concentrations in the sol phase of sputum were significantly higher at the time of the patients’ exacerbation visit compared with levels at baseline. Mean concentrations of TNF-α rose from 404 ± 169 pg/ml at baseline to 1.649 ± 526 pg/ml at the exacerbation visit (p = 0.01). Sputum TNF-α concentrations then declined significantly from exacerbation levels, to 426 ± 200 pg/ml, when measured 1 mo later (p = 0.01) (Figures 1, 2).

### IL-8 Concentrations
IL-8 concentrations were significantly higher at the time of the patients’ exacerbation visit compared with levels at baseline. Mean levels of IL-8 rose from 69.8 ± 26.1 ng/ml at baseline to 127.3 ± 46.2 ng/ml at the exacerbation visit (p = 0.05). Sputum IL-8 concentrations then declined significantly from exacerbation levels, to 67.2 ± 32.3 ng/ml, when measured 1 mo later (p = 0.04) (Figure 3).

### MPO Concentrations
Although there was a trend toward an increase in sputum MPO concentrations during exacerbations, the difference in MPO concentrations from exacerbation compared with base-

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### RESULTS

#### Subjects

Fifty-two subjects were screened for inclusion; however, two subjects were not able to successfully produce sputum at baseline and they were therefore not enrolled into the study. Of the 50 subjects who were recruited into the study, one subject was subsequently withdrawn because his baseline spirometry testing exceeded eligibility criteria (FEV₁ was 76% of predicted). Two patients were withdrawn several weeks after being enrolled when they admitted that they were still smoking. None of the three withdrawn patients suffered an exacerbation of COPD during the study follow-up period. The mean age of the 50 enrolled patients was 71.5 ± 10.0 yr, and 20% of the patients were female. The mean baseline FEV₁ (± SD) of the enrolled patients was 0.95 ± 0.31 L (39% of predicted).

<table>
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<th>Group</th>
<th>n</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Baseline FEV₁</th>
<th>Exacerbation FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled cohort</td>
<td>50</td>
<td>71.5 ± 10.0</td>
<td>40/10</td>
<td>0.95 ± 0.31</td>
<td>—</td>
</tr>
<tr>
<td>Patients who experienced a COPD exacerbation</td>
<td>14</td>
<td>71.6 ± 7.7</td>
<td>11/3</td>
<td>0.89 ± 0.24</td>
<td>0.85 ± 0.26 (35%)</td>
</tr>
</tbody>
</table>

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A COPD EXACERBATION (n = 14)

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### Table 1

**Characteristics of the Enrolled Subjects (n = 50) and of Those Who Experienced a COPD Exacerbation (n = 14)**
line was not statistically significant. Mean levels of MPO rose from 2,063 ± 1,300 ng/ml at baseline to 4,256 ± 2,717 ng/ml at the exacerbation visit (p = 0.14). Similarly, sputum MPO concentrations trended downward again 1 mo later, to 1,222 ± 491 ng/ml, but the decline was not statistically significant (p = 0.20) (Figure 4).

**Evidence for Acute Viral Infection**

Two patients met the serologic criteria for acute viral infection; one patient had a fourfold increase in titers against FluA, and the second patient had an acute seroconversion indicative of RSV infection (titers < 1:8 on the day of exacerbation to > 1:256 1 mo later). Both patients had positive PCR reactions for detection of virus. The first patient had FluA RNA detected from the sputum on the day of exacerbation, but not on the baseline or convalescent days’ visits. The second patient similarly had RSV RNA detected from the sputum on the day of exacerbation, but not on the baseline or convalescent days’ visits.

None of the other 12 patients showed serologic evidence of acute viral infection, and none of the other patients had viral nucleic acid detected at any time by PCR methods. Only one patient actually grew live virus in tissue culture; this patient grew enterovirus from his baseline sputum, but not from his exacerbation sputum, and this was therefore not thought to be clinically significant.

**Evidence for Acute Bacterial Infection**

An acute bacterial airway infection was defined as demonstration of a new pathogenic organism cultured from the sputum.
on the day of exacerbation, but not cultured at baseline. Only one patient met this criterion for an acute bacterial airway infection. This patient cultured $10^9$ Klebsiella species from his sputum on the day of exacerbation. Sputum cultures from this patient at baseline, and 1 mo later after therapy with antibiotics, did not grow the organism.

**Sputum Cytokine Concentrations in Patients with Documented Viral or Bacterial Exacerbations**

Changes in sputum cytokine concentrations for those patients with documented infection ($n = 3$), were compared with those patients in whom bacterial or viral infection could not be identified ($n = 11$). Patients with documented infection did not demonstrate greater increases in sputum levels of inflammatory cytokines during exacerbations compared to patients without demonstrable infection. Changes in sputum levels of MPO and IL-8 from the baseline to exacerbation visits were not significantly different in the two groups of patients ($p = 0.78$ and $p = 0.18$, respectively). Curiously, those patients with evidence of infection had a significantly smaller increase in sputum TNF-α concentrations during the time of acute exacerbation compared with those patients in whom infection was not identified ($p = 0.03$) (Figure 5).

**DISCUSSION**

Relatively little is known about the exact mechanisms of acute COPD exacerbation. Although airway inflammation is thought to play a key role in the pathogenesis of COPD exacerbation, the magnitude of the inflammatory response during periods of exacerbation has not been longitudinally studied in individual patients. Our study has clearly shown that individuals who experience an acute COPD exacerbation demonstrate elevated markers of airway neutrophilic inflammation relative to their clinically stable state. Sputum levels of IL-8 and TNF-α in-
increased significantly in patients at the time of exacerbation, and then fell again back to baseline levels 1 mo later, suggesting that the duration of the heightened inflammatory response was relatively short-lived in these medically treated patients.

Previous studies of bronchial biopsies from patients with chronic bronchitis and COPD have shown that airflow limitation is associated with an increased number of T lymphocytes and macrophages within the bronchial mucosa (1). More recent bronchial biopsy studies have shown that expression of the intercellular adhesion molecules ICAM-1 and E-selectin in the endothelium is upregulated in patients with COPD (20). TNF-α is a cytokine known to upregulate adhesion molecules (21), and the increased concentrations of TNF-α that we have observed at the time of COPD exacerbations may function to facilitate adhesion and migration of leukocytes through endothelial cells and into the bronchial mucosa at the time of COPD exacerbation.

IL-8 is a chemotactic cytokine produced by alveolar macrophages, lymphocytes, epithelial cells, and neutrophils which functions to recruit and activate neutrophils (22, 23). Increased local concentrations of this chemokine may explain the increased numbers of neutrophils found in the sputum of patients during times of COPD exacerbation.

Previous studies have shown that the granulocyte activation markers HNL and MPO are elevated in COPD patients’ sputum relative to control subjects (4). MPO is a protein that is released from the primary granules of neutrophils during neutrophil activation. Our study did show that sputum MPO did increase somewhat during the time of acute exacerbation, suggesting evidence of neutrophilic activation during episodes of COPD exacerbation; however, unlike the dramatic increases in TNF-α and IL-8, the increase in MPO did not reach levels of statistical significance.

It should be noted that the sputum was frozen before centrifugation and assay for cytokines. Freezing may theoretically cause cell disruption with release of intracellular mediators. Thus our results include measurements of both secreted and possibly cell-associated inflammatory cytokines.

The second objective of this study was to determine the causative infectious agent of our patients’ COPD exacerbations, and to correlate infection with markers of an increased neutrophilic inflammatory response. Traditionally, one difficulty in determining whether a COPD exacerbation is caused by bacterial infection has been the ability to differentiate between chronic bacterial colonization of the respiratory tract and actual acute infection (8, 9). We attempted to circumvent this difficulty by comparing sputum bacterial flora at the time of exacerbation with flora obtained during remission periods. Thus, an acute bacterial airway infection was defined as demonstration of a new pathogenic organism cultured from the sputum on the day of exacerbation. Using this definition we were able to document causative bacterial infection in one of 14 patients. This result was not entirely unexpected. Previous studies comparing tracheobronchial microflora during 77 COPD exacerbations with 628 remission specimens did not show significant differences in the number of positive sputum cultures (30% versus 22%) (24). Similarly, studies of transtracheal aspiration from patients with COPD taken during the stable state and during acute exacerbation have not shown significant differences in the number of positive bacterial cultures (25, 26). However, other investigators have done quantitative bacterial cultures from specimens obtained from lower airway protected brush sampling of patients with COPD and have shown that bacterial infection may account for up to 27% of acute COPD exacerbations (11). Presumably, the protected brush sampling technique may be more sensitive for detecting the presence of abnormal bacterial flora during acute exacerbations than induced sputum cultures.

Available data indicate that the association between respiratory virus infection and acute exacerbations of COPD is somewhat clearer than that with bacteria. Recent studies have implicated influenza virus and RSV as causing clinical exacerbations (10). A study from Gump and colleagues followed 25 patients with chronic bronchitis for 4 yr and was able to show using serologic evidence that 33% of 116 exacerbations could be related to viral infection with influenza, parainfluenza, RSV, and rhinovirus (9). Our study used serologic, viral culture and PCR techniques to detect evidence of acute viral respiratory tract infection. We were able to conclusively demonstrate acute viral infection in two of the 14 patients with COPD (14%) who had exacerbated.

Although we thoroughly searched for evidence of bacterial and viral infection in our patients with exacerbations, there are several possible limitations to this study. We did not examine for evidence of acute infection with chlamydia or mycoplasma. A 1991 study assessing antibody titers against TWAR (Chlamydia pneumoniae) had demonstrated that C. pneumoniae infection is rare in patients with acute exacerbation (27), and Gump’s 1976 study had observed only one COPD exacerbation of 116 that could be attributed to mycoplasma infection (9). However, a recent study of patients from the Netherlands has shown up to a 3% rate of acute chlamydial infection in 271 patients with COPD followed for a mean of 15 mo (28). Similarly a 1999 Turkish study of patients with acute COPD exacerbation observed that 6% and 8% of 49 patients had serologic evidence of acute Mycoplasma pneumoniae and C. pneumoniae infection, respectively (29). The two studies cited were European, and may not be generalizable to North American patients; however, based on the incidence rates seen in these studies, it is possible that our study may have failed to detect up to 14% of patients whose exacerbation may have been associated with acute infections with mycoplasma or chlamydia organisms.

Acute viral infections have been shown to increase airway responsiveness, and viral-induced airway epithelial damage is known to result in airway inflammation and edema (12). Viruses are also known to stimulate the release of IL-2 in asthmatics (30). Similarly, bacterial airway infections are associated with purulent sputum and sputum neutrophilia. We therefore hypothesized that patients with documented viral or bacterial infection would show higher concentrations of airway inflammatory cytokines than those patients in whom an infectious agent could not be identified. Although this study was only able to definitively identify a causative viral or bacterial organism in 3 of 14 patients, the patients with documented infection tended to have smaller increases in sputum levels of IL-8 and had significantly smaller increases in sputum TNF-α relative to patients who were not infected.

In summary, COPD patients with documented infection did not demonstrate greater increases in sputum levels of inflammatory cytokines during exacerbations compared with patients without demonstrable infection. We conclude that markers of airway neutrophilic inflammation increase at the time of acute COPD exacerbation and then decline 1 mo later, and that this acute inflammatory response appears to occur independently of a demonstrable viral or bacterial airway infection. Further research will be of value to determine whether concentrations of airway cytokines can be used in individual patients to monitor the course of COPD, and possibly to predict COPD exacerbations before they occur.

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References


