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Introduction: Chronic obstructive pulmonary disease (COPD) has been associated with lower airway, systemic, and, more recently, upper airway inflammation. The systemic component may be important through an association with increased cardiovascular comorbidity. While it is known that lower airway and systemic inflammation are increased at exacerbation of COPD (Ex)-COPD, it is not known whether the upper airway is involved at this time, nor how the upper airway, lower airway, and systemic compartments relate during such events. We investigated the relationships between systemic, upper airway, and lower airway inflammation at ExCOPD. **Method:** Serum, nasal wash, and sputum samples were obtained at 41 Ex in 41 subjects with COPD (mean [SD] age, 69.0 [7.7] yr; FEV₁, 1.00 [0.43] L). We assayed leukocytes, IL-6, IL-8, myeloperoxidase (MPO), and CRP. Pre-Ex baseline samples were available in 21 patients. **Results:** In addition to increases in systemic and lower airway inflammation, Ex were associated with greater upper airway inflammation (nasal leukocytes and IL-6, stable vs. Ex: 4.08 vs. 4.41 log₁₀ cells/ml, $p = 0.04$; 0.40 vs. 0.89 log₁₀ pg/ml, $p = 0.09$). There were significant correlations between the lower airway and systemic, and lower and upper airway inflammation, but not between the upper airway and systemic compartments: sputum leukocytes with serum IL-6 and CRP ($r = 0.38$, $p = 0.01$; $r = 0.39$, $p = 0.02$) and sputum IL-8 with serum IL-6 ($r = 0.37$, $p = 0.02$). Sputum MPO correlated with nasal leukocytes, IL-6, IL-8, and MPO: (all $r > 0.43$, $p < 0.01$), and sputum leukocytes with nasal IL-6 ($r = 0.38$, $p = 0.02$). Similar relationships were observed in paired data for changes in sputum leukocytes with changes in serum IL-6 and CRP. **Conclusion:** ExCOPD are associated with pan-airway inflammation, but the systemic inflammatory response is related to the magnitude of the lower rather than upper airway inflammation.

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Modulation of Airway Inflammation by *Haemophilus influenzae* Isolates Associated with Chronic Obstructive Pulmonary Disease Exacerbation

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Chronic obstructive pulmonary disease (COPD) is associated with periodic exacerbations that manifest as worsening of lung function and increased dyspnea, cough, sputum production, and sputum purulence. COPD exacerbations are associated with increased markers of inflammation in the airway, including neutrophils, interleukin(IL)-6, and IL-8 (1, 2). These observations led to the hypothesis that factors that promote airway inflammation lead to worsening airway function in patients with COPD. Although infection clearly has the ability to induce airway inflammation, the role that bacteria play in COPD exacerbations remains controversial (3, 4). Bacteria commonly colonize the airway of patients with COPD at baseline, making the presence of bacteria insufficient to explain worsening airway function (5–7). However, COPD exacerbation could be precipitated by an increase in bacterial number; change in the airway compartment in which bacteria are located; or acquisition of new, more virulent, and/or more proinflammatory bacterial species or strain (3, 8, 9). Nontypeable *Haemophilus influenzae* is the bacterial species most commonly isolated from airway samples during COPD exacerbations (9, 10). The ability of this bacteria to cause intense airway inflammation and the association of exacerbations with development of humoral immune responses to *H. influenzae* acquired for the first time supports a potential role for infection by this organism in causing COPD exacerbations (11). However, patient and bacterial factors that determine whether airway infection results in worsening of airway function are poorly defined.

We have previously reported an initial comparative study of *H. influenzae* isolates from patients with COPD who were followed as part of a prospective, longitudinal study at the Buffalo Veterans Affairs Medical Center (12). For this study, 17 bacterial isolates were obtained from 15 patients with COPD who underwent serial assessment of clinical status, sputum microbiology, and serum antibacterial antibody production. Exacerbation strains were defined as new isolates cultured from sputum during exacerbation of clinical symptoms with subsequent development of a homologous bactericidal serum antibody response. Colonization strains were not associated with an increase in symptoms or new antibody production. We found that strains of *H. influenzae* associated with exacerbations caused more airway neutrophil recruitment compared with colonization strains in an *in vivo* mouse model of airway infection. Experiments

using an *in vitro* model of human primary airway epithelial cells revealed that exacerbation strains adhered significantly more to epithelial cells. In addition, exacerbation isolates induced greater release of IL-8 compared with colonization strains, a response likely mediated by increased activation of both the nuclear factor- κ B and p38 mitogen-activated protein kinase signaling pathways. The results indicate that *H. influenzae* isolated from patients with exacerbations of COPD induce more airway inflammation, and likely have differences in virulence compared with colonizing strains.

We have gone on to investigate selected characteristics of the interaction between *H. influenzae* and airway epithelial cells that could account for bacterial strain differences in induction of IL-8. Previous experiments in our laboratory indicate that multiple soluble factors are released during epithelial cell interaction with *H. influenzae* that augment both IL-8 release and expression of other inflammatory mediators. Accordingly, we questioned whether these factors might disproportionately augment epithelial cell IL-8 levels in experiments using exacerbation strains or suppress IL-8 levels after epithelial cell interaction with colonization strains. However, we found that differences between *H. influenzae* isolates associated with exacerbation versus colonization in patients with COPD were not attributable to the presence of soluble factors generated after epithelial cell-bacterial interaction. Interestingly, induction of IL-8 expression by airway epithelial cell interaction with both exacerbation and colonization strains of *H. influenzae* was inhibited by exposure of epithelial cells to the macrolide antibiotics erythromycin and azithromycin. This effect was not due to antibacterial properties of these antibiotics, as inhibition of IL-8 expression was seen when bacteria were killed before experiments by pretreatment with gentamicin. Taken together, our findings support the concept that *H. influenzae* infecting the airway during COPD exacerbations mediate increased airway inflammation and contribute to decreased airway function. Furthermore, inflammatory mediator generation by epithelial cells exposed to bacteria in the airway may be modulated pharmacologically, and this strategy could improve airway function in patients with COPD.

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