treatment by monitoring sputum cell counts: effects on exacerbations. Eur Respir J 2006; (in press)
16 Lancet. Warnings for asthma drugs [editorial]. Lancet 2005; 366:266

Coinfection in Exacerbations of COPD

A New Frontier

Investigations with modern investigative techniques have clarified considerably the role of bacteria and viruses in the pathogenesis of exacerbations of COPD. Application of polymerase chain reaction-based methods for detection has shown that viral nucleic acids are present in respiratory secretions in 30 to 50% of exacerbations. Furthermore, these studies used sputum samples, rather than nasopharyngeal samples, as was done in previous studies, providing us with confidence that direct viral infection of the tracheobronchial tree is responsible for the exacerbation. Application of molecular epidemiology has demonstrated that acquisition of new strains of bacteria is critical to the pathogenesis of bacterial exacerbations. Other investigations have shown that specific immune responses and a neutrophilic inflammatory process accompany bacterial exacerbations. Typical and atypical bacterial pathogens are now implicated in up to 50% of exacerbations.

Though our knowledge of bacterial and viral exacerbation pathogenesis as sole agents has improved considerably, little is known about the consequences of coinfection with these infectious agents in COPD. In this issue of CHEST (see page 317), Wilkinson et al demonstrate that simultaneous identification of bacterial and viral pathogens in sputum at the time of exacerbation is associated with enhanced airway inflammation, increased bacterial load and symptoms, and a larger decrement in lung function. Their findings are interesting and valuable. However, this study has important limitations that should be considered in its interpretation. The only virus actively identified in this study was the rhinovirus. Identification of other viruses would have been useful; instead, cold symptoms were used as a surrogate. However, it is unclear how specific cold symptoms are for viral infection, as allergic and environmental stimuli can induce similar symptoms. Sera obtained before and after the exacerbation were available to the investigators. Demonstration of a serological response to viral antigens would have enhanced the pathogenic significance of the rhinovirus identified. It is difficult to draw conclusions regarding the pathogenic significance of bacterial pathogens isolated from sputum in the study. Specifically, the investigators did not attempt strain identification by molecular methods to distinguish between colonizing strains antedating the exacerbation and new acquisitions at the time of exacerbation. Demonstration of a serologic response to the infecting bacterial strain would have also been important.

Bacterial-viral interaction in the lower respiratory tract is best understood in the context of influenza and the development of secondary bacterial pneumonia. Similar mechanisms may exist in COPD exacerbations, including viral infection related impairment of innate and adaptive immune mechanisms as well as increased bacterial adherence to host cells. Mechanisms that are peculiar to COPD are also likely. The deleterious effects of viral infection of an already compromised mucociliary clearance could allow retention of secretions and bacterial overgrowth. Inflammation induced by the viral infection in an already inflamed airway could impair lung defense mechanisms, allowing establishment of bacterial infection. Mechanisms of bacterial-viral interaction are poorly understood in the context of COPD and warrant further investigation. Furthermore, most bacterial-viral interaction research has focused on the influenza virus, whereas in COPD, rhinovirus and respiratory syncytial virus infections are equally important.

The conventional paradigm is that an acute viral infection precedes and predisposes to the development of bacterial infection in the respiratory tract. However, an alternative paradigm may exist in COPD, in which bacterial infection may facilitate viral infection. Chronic bacterial infection of the lower airways in COPD is an inflammatory stimulus, and a chronically inflamed airway is likely to be more hospitable to viral pathogens. In fact, increased levels of baseline airway inflammation in COPD are associated with more frequent exacerbations.

In this study, a higher airway bacterial load as measured in sputum was seen in coinfections and during exacerbations as compared to stable state. Several issues surround the measurement of bacterial load: its significance and its interpretation. Two methods are used by investigators to assess airway bacterial load. In the first method, as in this study, all bacterial colonies isolated, pathogens and nonpathogenic species, are counted as contributing to the bacterial load. This method assumes that all bacteria isolated in sputum are coming from the lower respiratory tract. That is unlikely because some extent of
salivary contamination is inevitable in sputum samples, and saliva contains high concentrations of non-pathogenic species. Furthermore, in bronchoscopic studies, non-pathogenic microorganisms have not been associated with inflammation in the lower respiratory tract in COPD. The second method is to count colonies of potential bacterial pathogens only. This may be more reflective of the state of colonization of the lower respiratory tract. Even if bacterial load estimation in sputum reflects the lower respiratory tract milieu, it does not account for the wide variation in virulence among and within bacterial species. It is unlikely that *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Pseudomonas aeruginosa* strains at the same concentration will be equivalent inflammatory stimuli in the airway.

Another concern is whether statistically significant variations in load among groups shown in this and other studies are of enough magnitude to be biologically significant. These differences are often within 1 log (10-fold), whereas the total bacterial load in the airways is in the order of 7 to 8 logs. Therefore, these differences are actually quite small; for example, a 0.5 log difference is 7% of the total load.

It is possible that increased bacterial load and exacerbation are both related to new strain acquisition, rather than to each other. One could speculate that when new strains are acquired because of the lack of an effective host immune response, there is uninhibited growth of these strains in the airways, resulting in higher concentrations. Once an immune response develops, there is reduction in the airway concentrations of bacteria; therefore, lower concentrations are seen in stable disease. Though bacterial load undoubtedly contributes to the pathogenesis, it is unlikely to explain a very complex host-pathogen interaction that ultimately expresses itself in an exacerbation.

After decades of relegation to nuisance value, exacerbations of COPD are now recognized as major contributors to the clinical course of COPD. A better understanding of their complex pathogenesis should lead to more efficacious treatment and prevention strategies.

Sanjay Sethi, MD
Buffalo, NY

Dr. Sethi is an Associate Professor, Department of Medicine, Division of Pulmonary and Critical Care and Sleep Medicine, University at Buffalo SUNY, and Department of Veterans Affairs Western New York Healthcare System. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Sanjay Sethi, MD, Veterans Affairs Western New York Healthcare System (151), 3495 Bailey Ave, Buffalo NY 14215; e-mail: ssethi@buffalo.edu

REFERENCES