EDITORIAL

# Bronchial Colonization in Chronic Obstructive Pulmonary Disease: What's Hiding Under the Rug

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Bronchial colonization involves the presence of one or more microorganisms in bronchial mucosa in the absence of disease, a situation that is distinct from bronchial infection, in which the microorganisms proliferate and cause symptoms. In patients with chronic obstructive pulmonary disease (COPD) bronchial infection can be recognized as either exacerbation or pneumonia. Both exacerbation and pneumonia can be distinguished from latent bronchial infection, in which disease can be detected in the absence of respiratory symptoms when cultures of bronchial secretions are positive and cell and immunological markers, such as neutrophils or myeloperoxidase, provide evidence of an inflammatory response. Microorganisms such as *Streptococcus viridans* that are not considered potentially pathogenic in the respiratory tract because they are usually innocuous for an immunocompetent host may occasionally colonize the bronchial mucosa without causing a local inflammatory response. However, microorganisms that are usually considered pathogenic, such as *Haemophilus influenzae* and *Pseudomonas aeruginosa,* often do cause respiratory disease and when present in the bronchial mucosa in the absence of symptoms can cause a local inflammatory response that can be detected by examining respiratory secretions.[1,2] When such an inflammatory response is found, the clinical picture should be defined as latent bronchial infection to distinguish it from bronchial colonization, even though the latent infection will not necessarily progress to disease.

Twenty percent of all patient visits to a physician for acute respiratory symptoms are generated by patients with COPD.[3] The importance of COPD exacerbations, no matter what their cause, is made manifest by a mortality rate of nearly 20% in patients with severe COPD[4] in the weeks immediately following the episode, as well as by evidence that full lung function cannot be recovered in the months immediately following an exacerbation[5] and that loss of forced expiratory volume in the first second is greater in patients who experience more frequent exacerbations.[6,7] Studies examining the microbiology of COPD exacerbation have implicated one or more bacteria in the pathogenesis of over half of exacerbations.[8,9] *H influenzae* is the most commonly isolated agent in this clinical context,[10,11] although *Streptococcus pneumoniae* and *Moraxella catarrhalis* also cause exacerbation. The bacterial typology in patients whose forced expiratory volume in the first second is less than 50% of reference is somewhat different from that seen in patients with less severe disease, however. In the former, the prevalence of infection by *P aeruginosa* is higher.[9,11,12] Moreover, COPD exacerbation in such patients may present as pneumonia, seen in up to 8% of exacerbated patients for whom chest x-rays are taken.[13] Thus, the position that the etiology of COPD exacerbation must be considered infectious in most cases is based on the isolation of bacteria in over 50% of patients and on a prevalence of pneumonia approaching 10%. That interpretation justifies the use of antibiotics, which improve lung function in the days immediately following exacerbation and also reduce the rate of recurrence.[14] The improvement in lung function that comes with antibiotic treatment is slight and may not be perceived by patients with mild to moderate COPD; however, it is believed to play an important role in the course of COPD in patients with more severe disease.[15,16]

Treating COPD exacerbation with antibiotics sterilizes respiratory secretions and resolves infection in most cases,[17] but a quarter of patients who have followed such treatment develop bronchial colonization because of resistance to the prescribed antibiotic, persistence of a sensitive pathogen against which the antibiotic has not

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managed to have an effect, or early colonization by a new microorganism. Chodosh et al[8,19] examined the degree of sterilization of bronchial secretions achieved in over 400 patients with exacerbated chronic bronchitis, most of whom had COPD and initial sputum cultures that were positive for potentially pathogenic organisms and white cell differential counts with low percentages of epithelial cells. At the end of treatment, cultures were still positive in nearly a third of the patients, showing growth of the same microorganism initially isolated in 20% of the cases. Bacterial persistence was partly attributable to initial resistance to the antibiotic used (10%) or to resistance that was acquired early in the course of treatment (2%). Even so, in nearly 8% of patients the microorganism isolated had remained sensitive to the antibiotic, which was nevertheless ineffective. Early appearance of a new microorganism was responsible for positivity in 4%. A finding of positive respiratory secretion cultures at the end of treatment was accompanied by persistence of symptoms of exacerbation in fewer than 15%, and in the rest of the cases such a finding indicated bronchial colonization without symptoms leading to suspicion. That situation affected slightly more than a quarter of the patients who had been treated. Thus, it is not uncommon for the colonization that becomes evident after an episode of exacerbation to be caused by the same microorganism that triggered the exacerbation itself. Soler et al[9] also observed persistence of bacteria in respiratory secretions after antibiotic therapy in mechanically ventilated patients infected by *P aeruginosa.* The second most common cause of colonization soon after exacerbation is the appearance of a new microorganism in respiratory secretions, a situation seen in nearly 5% of patients who receive antibiotic treatment. Using a protected specimen brush, Monsó et al[20] also found bronchial colonization in nearly 25% of COPD patients during stable periods. *H influenzae* was the pathogen usually cultured in that study. Similar findings were reported by Zalacaín et al,[21] who used the same technique in patients who were more seriously ill. Finally, bronchial colonization by *H influenzae* or *S pneumoniae* has been observed even in COPD patients who have circulating antibodies against the colonizing bacteria.[22,23]

The so-called British hypothesis about the natural history of COPD maintains that the persistence of positivity in bronchial secretion cultures after recovery from an exacerbation may have an impact on clinical course and lung function. Groeneveld et al,[24] in a study of 16 COPD patients, observed that although *H influenzae* could persist in cultured bronchial secretions 5 months after the first isolation without causing exacerbation symptoms, in some patients such persistence would eventually lead to symptoms, based on the observation that *H influenzae* infections that developed during follow up were caused by the same *Haemophilus* strain that had been previously isolated in 50% of the cases. That observation suggested that bacterial persistence could partially explain recurrent *H influenzae* infections. Patel et al[25] obtained results along the same line in a cohort of 29 stable COPD patients, finding a higher incidence of exacerbation in subjects who initially had bronchial colonization. Additional insight into the role of bacterial persistence in respiratory secretions of asymptomatic individuals in the appearance of bronchial exacerbation was provided by Sethi et al,[26] who demonstrated that in the long term the development of symptoms was related more to acquiring a new bacterial strain in the bronchial tree than with the persistence of a pre-existing microorganism. That study followed patients for over 4 years, with molecular typing of the microorganisms that grew in airway secretion cultures.

Bronchial colonization, then, might be a result of both failure to sterilize bronchial secretions after an episode of exacerbation and to the growth of microorganisms new to the lower airway without the symptoms that are the hallmark of exacerbation. The absence of symptoms in patients with lower airways colonized by potentially pathogenic organisms might be related to bacterial load. In a recent study of quantitative cultures of bronchial secretions retrieved from COPD patients with a protected specimen brush, it was found that patients with symptoms of exacerbation had quantitatively higher bacterial loads than those who were stable,[27] suggesting that bacterial load in respiratory secretions was a determining factor in the development of symptoms. Stockley et al[28] used quantitative sputum cultures to study 89 exacerbated COPD patients with purulent sputum, finding a prevalence of upper respiratory tract infection exceeding 80% and high bacterial loads exceeding $10^8$ colony forming units per mL of sputum. The pathogen was eradicated in half the patients after treatment and bacterial load decreased substantially in those patients in whom sterilization of respiratory secretions had not been achieved by therapy.

Soler et al[2] observed that the presence of potentially pathogenic microorganisms in the respiratory secretions of patients with stable COPD might be associated with increased inflammatory cell counts and concentrations of tumor necrosis factor alpha in secretions, a profile that should be interpreted as latent infection rather than bronchial infection. In cases in which there is increased bacterial load due to overgrowth of a previously existing microorganism or to the introduction of a new one that manages to reach a high concentration in respiratory secretions after colonization, the bronchial bacterial load has been shown to be one of the determinants of bronchial inflammation. Hill et al[29] showed that a high bacterial load in respiratory secretions ($>10^6$ colony forming units per mL) during stable periods is associated with inflammation, marked by increased values of myeloperoxidase, elastase, interleukin 8, and leukotriene B4. They observed a dose-response relation between bacterial load and concentration of the aforementioned markers, consistent with the hypothesis that bacterial load determines inflammatory response even in asymptomatic individuals and that in some situations

bronchial colonization should therefore be considered latent infection. Along the same line, White et al[30] demonstrated that after a COPD exacerbation caused by infection, the persistence of bacteria in respiratory secretions was associated with an asymptomatic inflammatory response identifiable by high concentrations of diverse inflammatory markers, such as myeloperoxidase, elastase, and leukotriene B4, which is absent in subjects whose bronchial secretions were sterile. Likewise, a recent cohort study analyzing the impact of the appearance of new bronchial colonization in COPD patients showed that acquiring a new strain of a potentially pathogenic microorganism was associated with increased bacterial load and the development of bronchial inflammation, marked by increased levels of interleukin 8 in respiratory secretions and leading to worsening lung function that could be detected even in the absence of symptoms.[31] Therefore, bronchial colonization, whether caused by microorganisms persisting in respiratory secretions after exacerbation or by newly acquired bacterial flora in the bronchial tree, can cause a local inflammatory response to arise, even when symptoms are absent. The response will be greater when the bacterial load in respiratory secretions is greater and such cases should be considered latent bronchial infections.

The recent finding that bronchial colonization during stable periods is common in COPD and that it can generate a local inflammatory response when the bacterial load is high, even if only some patients develop exacerbation symptoms, has raised extremely interesting questions. Answering those questions—about the role of bronchial colonization in the natural history of COPD—will undoubtedly define new intervention approaches and improve prognosis. Once again, we will need to try to find whatever might be hiding under the rug.

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