Infections in "Noninfectious" Lung Diseases

Meghan E. Fitzpatrick[1], Sanjay Sethi[2,3], Charles L. Daley[4], Prabir Ray[1], James M. Beck[5], and Matthew R. Gingo[1]

[1]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [2]Deparment of Medicine, University at Buffalo, State University of New York, Buffalo, New York; [3]Department of Veterans Affairs, Western New York Healthcare System, Buffalo, New York; [4]Division of Mycobacterial and Respiratory Diseases, National Jewish Health, Denver, Colorado; and [5]Department of Veterans Affairs, Eastern Colorado Healthcare System, Denver, Colorado

Abstract

Many chronic pulmonary diseases, including those that are not primarily infectious in etiology, have some aspects of their pathogenesis that are influenced by infectious organisms. Microorganisms may contribute to chronic lung diseases, either directly (i.e., overt infection) or indirectly, via the amplification of inflammatory pathways that are critical to host defense. As techniques for detecting and characterizing microorganisms have advanced, investigations of both infecting and colonizing organisms have yielded new insights into mechanisms of pulmonary disease. In addition, changes in patterns of infection and microbial resistance have important implications for treatment. Examples of these infectious–pulmonary associations, including *Haemophilus influenzae* infection and chronic obstructive pulmonary disease, nontuberculous mycobacteria and bronchiectasis, and human immunodeficiency virus and obstructive lung disease, are reviewed.

Keywords: chronic obstructive pulmonary disease; bronchiectasis; nontuberculous mycobacteria; *Haemophilus influenza*; human immunodeficiency virus

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Correspondence and requests for reprints should be addressed to Meghan Fitzpatrick, M.D., 3459 Fifth Avenue, 628 NW MUH, Pittsburgh, PA 15213. E-mail: fitzpatrickme2@upmc.edu

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Due to the communication between the respiratory system and the environment, the lung is particularly vulnerable to microorganisms. Although microorganisms are likely most frequently considered in reference to acute pulmonary disease (e.g., pneumonia, acute bronchitis, or acute lung injury), they also play a role in chronic lung diseases. The importance of the lung microenvironment to chronic pulmonary diseases is an active area for investigation, particularly as new methods for detecting and characterizing microorganisms and describing the host response to local and systemic infection and colonization become available. This review describes interactions between microbe and host, and the implications for patient care, focusing on pathogens, including *Haemophilus influenzae*, nontuberculous mycobacteria, and human immunodeficiency virus (HIV), and their contributions to chronic obstructive pulmonary disease (COPD), bronchiectasis, and asthma.

Infection in COPD: the Role of Nontypeable *H. influenzae*

Historically, airway infection was associated with COPD as early as the 1950s, largely based on clinical observations and pathological observations at autopsy (1); however, the association between bronchial infection and obstructive lung disease was contentious for some time (2). Confirming and describing the precise relationships between infection and COPD has not been straightforward. Data in the current era of COPD have demonstrated a probable bidirectional relationship between COPD and bacterial infections, with each impacting the pathogenesis of the other. This association is frequently described via the "vicious circle hypothesis" (3), in which tobacco smoke or other respiratory irritants impair innate defenses, allowing microbial pathogens to persist and proliferate in the lower respiratory tract. These pathogens and their proinflammatory components worsen mucus hypersecretion, mucociliary dysfunction, and epithelial damage; furthermore, they trigger a cascade of adaptive immune responses, including macrophage activation and neutrophil recruitment. Thus, airway injury persists, allowing for further susceptibility to microbes and contributing to worsening airflow obstruction and/or lung parenchymal damage. Pathogenic organisms, such as nontypeable *H. influenzae* (NTHi), have now been

associated with both COPD exacerbations and COPD severity.

Exacerbations are of particular concern in COPD, given the unfavorable associations with quality of life, disease progression, healthcare expenditures, and mortality (4–7). Exacerbations are frequently seen in association with bacterial or viral respiratory infections; NTHi, rhinovirus, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* are the most commonly isolated pathogens (8). Although early studies of airway pathogens (including *S. pneumoniae* and *H. influenzae*) did not demonstrate a causal relationship between infection and exacerbation (9, 10) (including when considering bacterial load [11]), these studies were limited by their inability to detect the differing strains of bacterial species that may indicate a shift in the respiratory flora of a patient with COPD. In fact, when molecular characterization of bacteria became available, it was identified that acquisition of a new strain of NTHi or of the other major bacterial pathogens in persons with COPD was associated with increased risk of COPD exacerbation (12). It was subsequently confirmed that the immune response to NTHi is strain specific (e.g., the antibody-mediated immune response to an infecting strain does not provide future protection from infection/exacerbation with a strain with a different surface antigenic structure [13]). In further support of the vicious circle hypothesis, exacerbations of COPD in association with a new bacterial strain are associated with increases in systemic and local inflammatory mediators, including serum C-reactive protein and sputum TNF-α and neutrophil elastase. These increases were higher than those seen in exacerbations associated with pre-existing bacteria or with pathogen-negative exacerbations (14).

In addition to overt infection, bacterial colonization may also be associated with COPD progression. The standard definition of colonization is "presence of a pathogen that does not cause damaging effects to the host or elicit a host response" (8), implying that true colonization should be inconsequential. Our use of the term "colonization" in COPD to describe bacterial presence in the lung in the absence of symptoms of an exacerbation may therefore be incorrect, as there is accumulating evidence that this bacterial presence may in fact be associated with disease pathogenesis. In a study comparing healthy adults and stable ex-smokers with COPD, NTHi was present in bronchoscopic samples of 26% of persons with stable chronic bronchitis versus none in healthy adults. In addition, 33% of patients with stable COPD had NTHi identified in bronchial epithelium versus none in healthy adults. Interestingly, NTHi obtained from upper respiratory samples was, in several cases, different from lower respiratory samples, confirming that sputum alone may not adequately represent the microbial environment of the lung (15). To assess the association between lower airway colonization, COPD, and inflammation, a study investigating the lower airway flora and airway inflammation in ex-smokers with COPD, ex-smokers without COPD, and healthy nonsmokers was performed (16). First, common respiratory pathogens were recovered significantly more frequently in participants with COPD (34.6% vs. 0% ex-smokers vs. 6.7% non-smokers at 100 bacteria/ml), and the most frequently recovered isolate with NTHi. Overall, persons with COPD had increased airway neutrophilia and increases in inflammatory mediators and proteinases, including IL-8, leukotriene B4, and matrix metalloproteinase-9. When persons with COPD with and without bacterial colonization were compared, colonized individuals demonstrated increases in neutrophilia, IL-8, IL-10, active matrix metalloproteinase-9, and endotoxin (16). Most recently, a prospective longitudinal study in the Department of Veterans Affairs cohort has related colonization to symptoms; persons with COPD had significantly worse respiratory symptoms on the Breathlessness, Cough, and Sputum Scale (and higher levels of IL-8) when colonization was detected than during noncolonized periods (17). These data suggest that lower airway colonization is common in COPD, is associated with inflammatory changes, and is, in fact, consequential for patient outcomes.

Host response to NTHi and other bacterial infections likely drives some portion of the susceptibility to microbial impact. Persons with COPD have decreased phagocytic capability of alveolar macrophages, and may be less able to effectively clear respiratory bacteria (18). This phagocytic dysfunction was recently described to associate with COPD severity (19). Macrophages from healthy nonsmokers and persons with COPD (ex-smokers and active smokers) were obtained by bronchoalveolar lavage; *in vitro* phagocytosis of NTHi was found to be diminished in participants with COPD, particularly the active smokers. These findings also held true for *M. catarrhalis*, though not for *S. pneumoniae* or for inert particles, suggesting that the phagocytic defect is, to some degree, organism specific. Interestingly, in the group of participants with COPD, the phagocytic defect was greater for NTHi than for *M. catarrhalis*. Finally, the degree of phagocytic impairment for NTHi and *M. catarrhalis* was correlated with severity of airflow obstruction, as measured by FEV_1 % predicted (19). The direction of this association has yet to be established, but one hypothesis is that persistence of NTHi, facilitated by compromised phagocytic clearance, may contribute to persistent airway inflammation among active and ex-smokers with COPD.

In summary, the understanding of the relationship between bacteria and COPD has changed over time, in part due to advances in microbial detection and identification. Clinical and subclinical bacterial infection remains a common comorbid condition of COPD, and both infection and colonization with lower respiratory pathogens (particularly NTHi) are associated with inflammatory changes in the host. Further understanding of host–pathogen interactions in COPD may lead to new avenues for intervention, which are very much needed in this disease.

Infection in Bronchiectasis: Nontuberculous Mycobacteria

The term "bronchiectasis" derives from the Greek words *bronkhia* (denoting branches of main bronchi) and *ektasis* (stretching), and refers to the abnormal dilatation of airways caused by destruction of the muscular and elastic components of their walls. Laennec first described bronchiectasis in 1819 (20), and, 100 years later, A. J. Jex-Blake delivered a lecture at the Hospital for Consumption on the condition (21). He estimated that bronchiectasis was present in 2% of the hospital's admissions, and that the condition was usually the result of another lung disease, such as pneumonia, chronic bronchitis, or bronchial obstruction. Today, we are aware of many

causes of bronchiectasis, but all result in dilated, inflamed airways, often leading to chronic production of mucopurulent sputum, persistent bacterial colonization, and recurrent respiratory infections.

With the introduction of antibiotics and childhood vaccines, the incidence of bronchiectasis declined during the 20th century; however, a recent study evaluating a 5% sample of Medicare Part B beneficiaries reported that the prevalence of bronchiectasis is increasing in the United States (22). The overall average annual prevalence of bronchiectasis was 370 per 100,000 person-years, and increased 8.7% annually over the study period of 2000–2007. The prevalence rate was higher in women than in men, and increased with age: women aged 80–84 years had an average annual prevalence of over 500/100,000. Although the reasons for the increases are not known, it is clear that pulmonologists will be seeing more patients with bronchiectasis than in the recent past.

Bronchiectasis is characterized by a cycle of infection and inflammation that leads to worsening airway damage (23) (Figure 1). To break this cycle, investigators have used anti-inflammatory drugs, such as macrolides, to reduce inflammation with the hope of improving symptoms and pulmonary physiology and decreasing infectious exacerbations. The use of azithromycin in patients with cystic fibrosis (CF) who have chronic *Pseudomonas* infection has been shown to improve FEV_1, decrease exacerbations, and increase weight compared with placebo (24). Recently, three studies evaluated the benefits of chronic macrolide use in patients with non-CF bronchiectasis. In the Effectiveness of Macrolides in patients with BRonchiectasis using Azithromycin to Control Exacerbations (EMBRACE) trial conducted in New Zealand, patients with non-CF bronchiectasis were randomized to receive either 500 mg azithromycin (n = 71) or placebo (n = 70) three times per week (25). The rate of event-based exacerbations was 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group (rate ratio of 0.38 [95% confidence interval = 0.26–0.54]). In the Bronchiectasis and Low-dose Erythromycin Study (BLESS) trial in Australia, similar patients were randomized to 400 mg erythromycin (n = 59) or placebo (n = 58) twice daily (26). Erythromycin significantly decreased pulmonary exacerbations from 1.97 to 1.29 per patient per year (rate ratio 0.57 [95% confidence interval = 0.42–0.77]). Finally, the Bronchiectasis and Long-term Azithromycin Treatment (BAT) trial in the Netherlands randomized patients to receive 250 mg azithromycin (n = 43) versus placebo (n = 40) given daily (27). Azithromycin use was associated with a lower median number of exacerbations than placebo (2 versus 0, $P < 0.001$). Although these studies varied in the macrolide used, dosage used, and number of exacerbations required to enter the study, they all showed benefits to chronic macrolide therapy when used for 6–12 months.

Unfortunately, the improved outcomes have come with a price—the acquisition of macrolide resistance. In the EMBRACE trial, macrolide resistance testing was not performed routinely, but at least two patients had developed macrolide-resistant *Streptococcus* pneumonia at 6 months (25). A total of 28% of those in the BLESS trial on erythromycin acquired macrolide resistance in oropharyngeal streptococci compared with 0.04% of those on placebo (26). In the BAT trial, 85% of those on azithromycin acquired macrolide resistance in bacterial pathogens versus 26% of those on placebo (27). The clinical importance of this resistance is not yet known; however, macrolides are used to treat many of the organisms that are typically isolated in patients with bronchiectasis, such as *H. influenzae*, *Moraxella catarrhalis*, *S. pneumonia*, *Staphylococcus aureus*, and nontuberculous mycobacteria (NTM) (25–28).

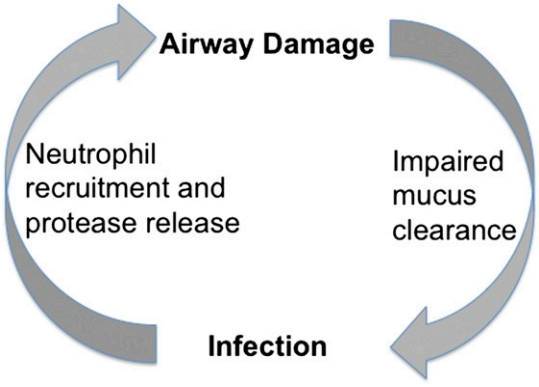

Figure 1. Inflammatory cycle of bronchiectasis.

Pulmonary NTM infections are increasing in the United States and other industrialized countries. Using the same Medicare population for the study of bronchiectasis, investigators reported significant increases in pulmonary NTM infections from 1997 to 2007 (29). Overall, there was an 8.2% per year increase in the incidence of pulmonary NTM; as with bronchiectasis, the rates were higher in women than in men. In this study, 44% of the patients with NTM also had bronchiectasis (29). The frequency of NTM isolation in non-CF bronchiectasis has varied from 2 to 30% (Table 1); *Mycobacterium avium* complex (MAC) is the most common isolate, followed by rapidly growing mycobacteria (30–34). Thus, the overlap between bronchiectasis and NTM infections is significant, and both conditions appear to be increasingly prevalent.

Treatment of most NTM species is largely dependent on macrolide-containing regimens, and loss of the macrolide from the treatment regimen is associated with very poor treatment outcomes (34). Among 51 patients with macrolide-resistant disease at the University of Texas, sputum conversion occurred in 78% of patients who received a parenteral aminoglycoside and lung resection versus 5% who did not (35). The 1-year mortality in patients who remained culture positive was 34% compared with 0% in those who converted cultures to negative. The main risk factor for resistance was macrolide monotherapy. Clearly, loss of the macrolide from the treatment regimen was disastrous.

Treatment of *Mycobacterium abscessus* consists of administration of a macrolide along with intravenous imipenem (or cefoxitin or tigecycline), amikacin, and potentially other drugs with demonstrated *in vitro* activity (34). Culture conversion lasting at least 1 year occurs in 25–58% of patients with *M. abscesuss* infection (36–38), and, as with *M. avium* complex treatment, outcomes are worse when a macrolide cannot be used. In a study from

Table 1. Frequency of nontuberculous mycobacteria in non–cystic fibrosis bronchiectasis

Study	Site	*N*	NTM *n* (%)	Species (number of instances of each isolate)
Wickremasinghe and colleagues, *Thorax* 2005	Royal Brompton	100	2 (2)	MAC (2)
Fowler and colleagues, *Eur Respir J* 2006	Papworth	98	10 (10)	MAC (3) *Mycobacterium fortuitum* (3) *M. xenopi* (3) *M. malmoense* (1) *M. chelonae* (1) *M. simiae* (1) *M. terrae* (1)
McShane and colleagues, *Chest* 2012	University of Chicago	106	9 (8.5)	MAC (7) *M. chelonae* (1) *M. kansasii* (1)
Mirsaeidi and colleagues, *Int J Infect Dis* 2013	University of Illinois	182	55 (30)	MAC (55) *M. chelonae* (7) *M. kansasii* (2)

Definition of abbreviations: MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria.

South Korea, only 17% of patients with an isolate that was resistant to clarithromycin converted their cultures to negative compared with 64% of patients whose isolate was intermediate to susceptible (36). Interestingly, patients with *M. abscessus* subspecies *massiliense* were more likely to respond to treatment than those with *M. abscessus* subspecies *abscessus*. Although the reasons for this difference in response are not fully understood, it is likely due to the presence of a functional erm(41) gene in subspecies *abscessus*, which results in inducible macrolide resistance, whereas, in subspecies *massiliense*, the erm(41) gene is nonfunctional, so inducible resistance does not occur. If this explanation is correct, then loss of the macrolide would be expected to worsen treatment outcomes in patients with subspecies *massiliense* more so than in those with subspecies *abscessus*.

The rising prevalence of bronchiectasis coupled with increasing use of macrolides will inevitably lead to more macrolide resistance in bacterial pathogens. For the increasing number of patients with NTM pulmonary infections, this resistance will result in significantly worse treatment outcomes and, in some cases, incurable disease. To lessen this burden, we must be vigilant to ensure that patients do not have NTM infections before initiating macrolide therapy, and if an NTM is isolated during the course of macrolide therapy, the drug should be stopped. Otherwise, not only will rates of bronchiectasis and pulmonary NTM infections increase, but we will also almost certainly encounter increasing rates of macrolide-resistant NTM infections.

Obstructive Lung Disease: Associations with HIV

HIV infection has long been associated with pulmonary disease, since the first description of acquired immune deficiency syndrome presenting as *Pneumocystis* pneumonia in 1981 (39). Effective treatment for HIV, which typically involves combination antiretroviral therapy (cART), has changed the epidemiology of HIV and the associated pulmonary comorbidities. Whereas infectious lung diseases have fortunately declined in the era of cART (40), pulmonary disease persists. Current studies find that HIV is associated with increased risk for chronic lung conditions, such as lung cancer, pulmonary hypertension, interstitial lung disease, and COPD (41). As the epidemiology of lung disease in HIV has shifted toward more chronic lung conditions, the mechanisms of these associations are also being investigated.

Morbidity related to obstructive lung disease is common in HIV-infected persons. In the Pittsburgh HIV Lung cohort, respiratory symptoms and inhaler use are quite common, with over 50% of participants having at least one clinically significant respiratory symptom and 27.5% reporting using an inhaler in the previous year (42). Pulmonary function studies in HIV-infected persons show that 8.6–20% have airflow obstruction, and 10% have a positive response to bronchodilator (>200 ml and 12% increase in either FEV_1 or FVC) (42, 43). Although many of these abnormalities are more frequent in smokers, they are still quite common in never-smokers; in particular, bronchodilator response does not differ by smoking status. The findings related to bronchodilator responsiveness are of interest, as they may reflect airway hyperreactivity or asthma. Although there has been increasing focus on the development of COPD in this population, asthma has remained understudied despite its frequency in the general population and its apparent increased prevalence among those with HIV.

Before cART, asthma and airway hyperreactivity were common in HIV infection and related to smoking and possibly to atopy (44, 45). In the cART era, findings regarding the prevalence of asthma are uncertain. In the Veterans Aging Cohort Study, a predominantly smoking older male cohort, asthma diagnosis was similar between individuals with and those without HIV (41). Two recent studies with a broader population of individuals with HIV have found that 11 and 21%, respectively, have an asthma diagnosis by history (doctor-diagnosed asthma) (46, 47). These prevalence estimates may be greater than the estimated prevalence of approximately 7.6% in the general population (48). There was also 4 and 9% bronchodilator reversibility by American Thoracic Society/European Respiratory Society criteria in the two studies, respectively, again reflecting disease

prevalence that may be higher than expected in the general population (49).

The causes of these apparent increases in asthma and airway disease remain unclear, but recent studies have examined characteristics of asthma in HIV. In the Pittsburgh HIV Lung cohort, 55% of participants with doctor-diagnosed asthma reported onset of asthma in adulthood, often after diagnosis of HIV (47). In contrast, the majority of asthma diagnoses in the general population occurs in children (50). Doctor-diagnosed asthma was associated with female sex, obesity, not being on cART during the study period, and a history of bacterial or *Pneumocystis* pneumonia (47). In addition, approximately 10% of the cohort had high sputum eosinophil counts, and there was an association between doctor-diagnosed asthma or bronchodilator response and high sputum eosinophil counts, but the majority of participants with doctor-diagnosed asthma or bronchodilator response did not have elevated sputum eosinophils, suggesting that there may be non–T helper type 2–related mechanisms causing asthma in HIV. There were associations between asthma diagnosis or bronchodilator response and sputum and serum cytokines that were also related to chronic HIV infection: regulated upon activation, normal T cell expressed and secreted and macrophage inflammatory protein-1α and -1β (51). These findings, taken together, suggest that the later-onset asthma phenotype in HIV may be different than that seen in the general population, and that HIV-specific inflammatory factors may be related to disease pathogenesis. In addition, allergy/atopy, metabolic disease related to obesity, and predilection for respiratory infections could be important mechanisms causing airway inflammation in HIV.

Chronic airway disease has become an important comorbidity in individuals with HIV infection. There is a high prevalence of symptoms and inhaler use related to airway disease, such as COPD and asthma, in individuals with HIV infection. There may be HIV-specific risk factors associated with lung inflammation, leading to airway disease and asthma in this population, which need to be further studied to best prevent and treat airway disease in the HIV population.

Conclusions

This review highlights the importance and the complexity of the interactions between host and pathogen in "noninfectious" lung diseases, including COPD, bronchiectasis, and asthma. Although antibiotic therapies are increasingly used to treat the infectious comorbidities of COPD and bronchiectasis, in particular, these avenues of therapy come with the risk of antibiotic resistance. As more sophisticated methods of investigating the local and systemic resident flora in states of health and disease become available, new and refined analyses of the interactions between the immune system, microbiota, and inflammatory pathways will almost certainly shed new light on disease pathogenesis, and hopefully present novel approaches for modifying disease progression in pulmonary patients with "noninfectious" lung disease. ■

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