Role of Infections

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KEYWORDS

• Infection in COPD • Airway colonization • Chronic infection • New strain exacerbations
• Pneumonia and COPD • Innate immunity in COPD • Virulence factors • Vicious-circle hypothesis

KEY POINTS

- Infection and chronic obstructive pulmonary disease (COPD) can be regarded as comorbid conditions, because infections contribute the progression of COPD, and COPD alters the susceptibility and manifestations of lung infections.
- The underlying mechanism of acute exacerbations of COPD is acquisition of new strains of bacteria and viruses. A complex host-pathogen interaction then determines the clinical manifestations and outcomes of such acquisition.
- COPD predisposes to community-acquired pneumonia and alters its cause, treatment, and outcomes.
- Several lines of evidence now suggest that chronic airway infection by bacteria is prevalent in COPD, and by triggering a chronic inflammatory response contributes to progression of disease.
- Lung innate immune defenses are impaired in COPD, making these patients more susceptible to infection. Respiratory pathogens prevalent in COPD use various mechanisms to evade host responses and thereby cause acute and persistent infections.

INTRODUCTION

The role of infection in chronic obstructive pulmonary disease (COPD) was first postulated in 1953 by Stuart-Harris and colleagues[1] in what is now known as the British hypothesis. They speculated that the decline in the lung function in COPD was the result of mucus hypersecretion and recurrent bacterial infections. In the next 2 decades, several studies were performed to confirm the hypothesis. In some of these studies, sputum microbiology was used to compare the rate of bacterial infection in patients with chronic bronchitis at baseline and during exacerbations, as well as in comparison with individuals without COPD.[2–7] Some differences in bacterial infection related to disease state were found; for example, Smith and colleagues[2,3,8] found increased colonization with *Haemophilus influenzae* in patients with severe COPD compared with mild COPD. However, for the most part, differences in the rate of bacterial isolation from sputum at stable state (ie, colonization) versus at acute exacerbation (ie, infection) were not seen in these studies. Advanced molecular biology techniques to differentiate bacterial strains within species had not been developed and were therefore not available to these investigators. Other investigators examined this hypothesis by using serologic studies to determine levels of antibacterial antibodies in patients with chronic bronchitis. These results were also confusing and contradictory and were confounded by the use of laboratory strains as an antigen (discussed in Ref.[9]). In 1977, Fletcher and colleagues[10] published a landmark study that showed

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that frequency of exacerbations and mucus hypersecretion did not result in faster decline of lung function in patients with COPD. By the early 1980s, because of these observations and the appreciation of the importance of tobacco smoke in COPD pathogenesis, the British hypothesis was rejected, and bacterial infection was relegated to an epiphenomenon in this disease.[7]

The role of viral infection in COPD exacerbations was also extensively investigated in the 1960s and 1970s with viral cultures and serology at exacerbation.[3,5,8] Because of the lack of confounding by chronic colonization and serologic cross reactivity, about 30% of exacerbations were confirmed to be of viral origin. Following 20 to –30 years of scant investigation, the role of infection has been revisited in the last 2 decades with new molecular biology, immunology, and microbiology techniques.[11] Understanding of infection in COPD, both in the acute and chronic settings, has consequently developed substantially, as discussed later (Fig. 1).

ACUTE INFECTION

Acute infections in COPD are clinically recognized either as exacerbations or as episodes of pneumonia. The differentiation between the two presentations is based on the presence (pneumonia) or absence (exacerbation) of lung parenchymal involvement, which presents as an infiltrate on chest radiology. Although pneumonia has been always considered to be a more significant acute infection, exacerbations occur with much greater frequency and also have serious consequences in COPD. As the British hypothesis was being largely discredited, the importance of exacerbations in COPD was also minimized. They came to be regarded as self-resolving viral illness of little consequence (chest colds) for which no specific therapy was available and that were part of the natural course of the disease. The last 2 decades have seen considerable revision in this point of view, because data have emerged that exacerbations do contribute to the loss of quality of life and lung function in COPD and account for as much as half the cost of care of COPD. Furthermore, bacterial infection contributes to exacerbations, specific therapies are of benefit, and prevention of exacerbations is possible and is an important therapeutic goal in COPD.

Causes of Exacerbations

Exacerbations of COPD are airway inflammatory events that are induced by infection in most instances. The aggravating infection can be viral, bacterial, or a combination of viral and bacterial infections. Although there are episodes that are induced by poorly understood noninfectious factors, infections likely account for about 80% of exacerbations (Table 1).

Virus

The role of viruses in exacerbation was established in older studies (as discussed earlier) by viral culture and serology. Understanding of viral exacerbations has recently been expanded by the use of molecular diagnostic techniques and with the development of a human experimental model of rhinoviral exacerbations. The most common viruses detected in airway secretions at exacerbation are rhinovirus, influenza, respiratory syncytial virus (RSV), parainfluenza, and adenovirus. A recent systematic review found that viruses were detected in 34.1% of exacerbations.[12] More recent studies using molecular detection of virus

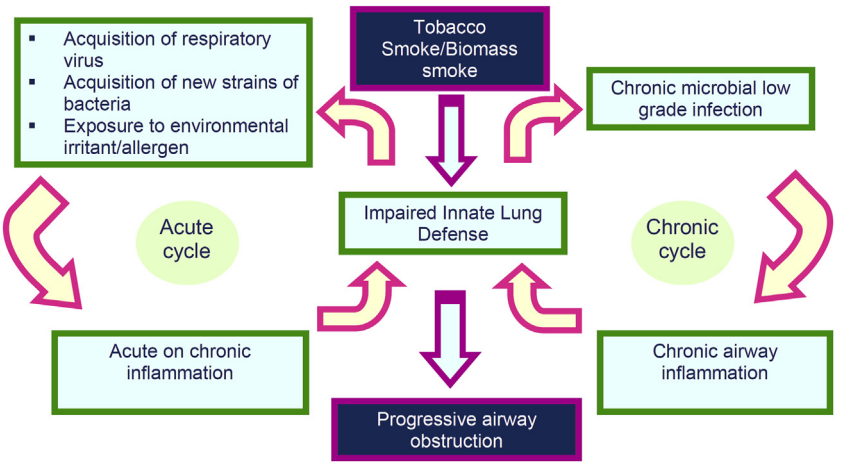

Fig. 1. Acute and chronic infection cycles in the pathogenesis of COPD.