# Respiratory Viral Infections in Chronic Lung Diseases

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**KEYWORDS**

• Chronic lung diseases • Respiratory viral infections • Chronic obstructive pulmonary disease • Cystic fibrosis • Interstitial lung diseases • Asthma

**KEY POINTS**

- Respiratory viruses remain to be important in the pathogenesis of chronic lung diseases.
- Respiratory viruses play an important role in chronic lung diseases, such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis, especially in disease exacerbations.
- There is not much evidence for the association of respiratory viruses with idiopathic pulmonary fibrosis or sarcoidosis.
- Preventive measures are needed to limit such viral infections, with good hand hygiene, avoidance of sick contacts, and viral vaccinations recommended for patients suffering from chronic lung diseases.

## INTRODUCTION

Chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), and interstitial lung diseases (ILD), affect many individuals worldwide. Patients with these chronic lung diseases are susceptible to respiratory lung infections and some of these viral infections can contribute to disease pathogenesis. This review highlights the associations of lung infections and the respective chronic lung diseases and how infection in the different lung diseases affects disease exacerbation and progression.

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is one of the leading causes of mortality and morbidity worldwide.[1,2] Among several risk factors, cigarette smoking is the most important one. However, smoking alone does not explain all the aspects of COPD. COPD can develop even in nonsmokers, especially in the context of biomass exposure in some parts of the world. More than half of smokers do not develop COPD. A subset of patients with COPD exhibits persistent inflammation despite smoking cessation.[3,4] In addition, accelerated loss of lung function may occur independent of smoking and occur with acute COPD exacerbations.[5] It is important to elucidate additional contributive factors besides smoking to control the disease. COPD is characterized by chronic inflammation of the small airways. Respiratory tract infection is an important cause of acute exacerbation and progression of the disease.[6]

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### *Common Viral Infections and Chronic Obstructive Pulmonary Disease Exacerbations*

Historically, bacteria have been considered the main infectious cause of COPD exacerbations.[7] A growing body of evidence, however, implicates viral upper respiratory tract infections (URIs) as the predominant risk factor associated with exacerbations of COPD.[8] Approximately 40% to 60% of all COPD exacerbations are associated with upper respiratory infections (URIs) and viral infections have been suggested to be important contributors to COPD exacerbations.[9] In fact, it has been shown that respiratory viruses, including rhinovirus, influenza, and respiratory syncytial virus (RSV) cause COPD exacerbations.[10–12] These exacerbations are more severe, last longer, and are associated with more heightened airway and systemic inflammatory responses than exacerbations due to other nonviral causes.[13–15] These differences cannot be attributed solely to pulmonary structural alterations in patients with COPD because healthy smokers also experience exaggerated symptomatic responses after viral infections.[16–18]

Detection rates of virus in COPD exacerbation are variable between approximately 22% and 64%.[9,11,19–27] The detection rates depend on onset to presentation, type of samples, and season. The most commonly identified viruses in exacerbation of COPD include rhinovirus, influenza viruses, RSV, parainfluenza, adenovirus, metapneumovirus, and coronavirus. Among them, rhinovirus and metapneumovirus are the most common viral pathogens in studies using polymerase chain reaction (PCR).[12,13,25] In these studies, rhinovirus was detected in 8% to 44% in the events of COPD acute exacerbation. Influenza vaccination rate can also affect the prevalence. A Hong Kong study showed that influenza was the most common virus in hospitalized patients with COPD; meanwhile, a cohort from a London outpatient clinic showed low prevalence due to relatively high influenza vaccination rate (74%).[11,15] Many COPD exacerbations also include virus and bacteria coinfection. Approximately 25% of the hospitalized patients with COPD exacerbations showed coinfection. The clinical impact of coinfection is longer hospital stay and severe functional impairment.[28]

Symptoms of COPD exacerbation include cough, increased sputum volume and purulence, and dyspnea; however, it is not easy to differentiate viral and nonviral causes of COPD exacerbation by symptoms. Typical “common-cold” symptoms, including fever, nasal congestion, or rhinorrhea, are prevalent in patients with COPD when virus is detected, but those symptoms also can be noted in nonviral exacerbation, so their usefulness in diagnosis remains limited.[13,29] Sputum purulence has been suggested as evidence for bacterial infection in COPD exacerbation, but sputum also can be purulent due to neutrophilia irrespective of causal organism.[30] Furthermore, almost all COPD exacerbations can be marked with change in sputum characteristics.[31] Therefore, the sputum characteristics are not a useful marker to differentiate viral and bacterial infection. On the other hand, sputum purulence may be used to decide the usage of antibiotics.[32] Although neutrophils are the predominantly increased cell type in sputum during COPD exacerbations, one report showed increased eosinophilia during viral exacerbations.[28] Viral exacerbations also are associated with frequent exacerbations, severe exacerbations, and a prolonged time for symptom recovery.[13] Viruses also can be detected in stable COPD. Patients with RSV infection had higher plasma fibrinogen, serum interleukin (IL)-6, and hypercapnia in stable state.[13] This suggests that asymptomatic viral colonization can potentially have a role in chronic inflammation and disease progression of COPD. Another study that supports this showed a relationship between frequent RSV detection and accelerated lung function decline (101.4 mL/y vs 51.2 mL/y, $P = .01$).[33] It has been proposed that the alveolar epithelial cells of smokers and patients with severe emphysema are more frequently latently infected with adenovirus as compared with smokers without airflow obstruction.[34,35] They found COPD lung epithelial cells express adenoviral E1A protein, and that this was associated with specific lung inflammation. The investigators propose such adenoviral infections in patients with COPD contribute to the amplification of the lung inflammatory responses.

PCR of respiratory samples is the main tool to detect causal viruses. Before the widespread use of PCR technique, low virus-detection rates underestimated their role in COPD. The introduction of PCR helped revolutionize viral diagnostics; PCR is far more sensitive and equally specific to the traditional techniques that include culture, antigen-detection tests, and serology.[36,37] Rhinovirus is one of the most common viruses in COPD exacerbation, but it is difficult to culture and serology is not possible due to the presence of more than 100 serotypes. Without PCR, these viruses cannot be identified. As a result, early studies using other diagnostic methods underestimated the prevalence of rhinovirus.[15] Among various methods to obtain samples, such as nasal lavage, throat swab, or induced sputum, it is not yet evident which method is superior. Some viruses, especially RSV, can directly invade the