

Viruses and exacerbations of chronic obstructive pulmonary disease: unmet clinical need

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Abstract

Chronic obstructive pulmonary disease (COPD) is a non-communicable long-term condition characterised by accelerated lung-function decline and intermittent episodes of respiratory illness called exacerbations. We discuss the current understanding of the role of viruses in these elements of COPD. The burden of acute viral illness in COPD is great and largely unrecognised. Because naturally occurring exacerbations are inherently difficult to study, only recently have we understood underlying pathophysiological mechanisms and the true prevalence of viral exacerbations. Data are also emerging to support a potential role for chronic viral infection in the progression of stable COPD. As knowledge in these two areas develops, it is clear that the role of viruses in COPD represents a significant unmet clinical need.

Keywords: chronic obstructive pulmonary disease, COPD, lung function, exacerbations

Introduction

Chronic obstructive pulmonary disease (COPD) is the end result of a genetically susceptible individual being exposed to sufficient environmental stimulus, invariably cigarette smoke in the developed world. The natural history of progressive, accelerated decline in lung function results in worsening symptoms and functional limitation. Patients are also variably predisposed to acute episodes of respiratory illness termed exacerbations, and it is exacerbations that are responsible for much of the morbidity, mortality and healthcare costs associated with COPD. COPD is an example, par excellence, of a non-communicable long-term condition, set to be the third commonest cause of death in the world by 2020. Why is this of any relevance to the virologist?

First, it is now apparent that respiratory viruses are a major cause of COPD exacerbation. The traditional view has been that exacerbations are typically caused by bacterial infection, with little significance attributed to viral aetiology as exemplified by the enthusiastic use of antibiotics. This view was formed in the context of poorly sensitive viral diagnostic tests, the absence of drugs effective against respiratory viruses and based on studies examining naturally occurring exacerbations. Such study design is problematic because once an exacerbation has presented, any preceding viral infection may already have been missed. In addition, the observation of bacterial, viral and mixed bacterial–viral pathogens in samples has complicated our views on aetiology. Seemingly at odds with this bacterial orthodoxy is the observation that over 50% of exacerbations are preceded by a cold [1], and that exacerbations are seasonal, reflecting the circulation of respiratory viruses.

The true burden of viral exacerbations has become apparent over the last 15 years following the use of more sensitive molecular diagnostics. Using these techniques, a putative viral aetiology has been identified in sputum samples from patients at exacerbations in around half of cases [2] (although the reported range is wide) with viruses disappearing from sputum in convalescence [2]. Rhinovirus is the most abundant, followed by respiratory syncytial virus (RSV) and influenza, with a number of other respiratory viruses occurring less frequently (Figure 1) [3]. Results from studies where convalescent patients act as their own controls strongly suggest an important role for acute viral infection in exacerbations of COPD, but evidence remains circumstantial.

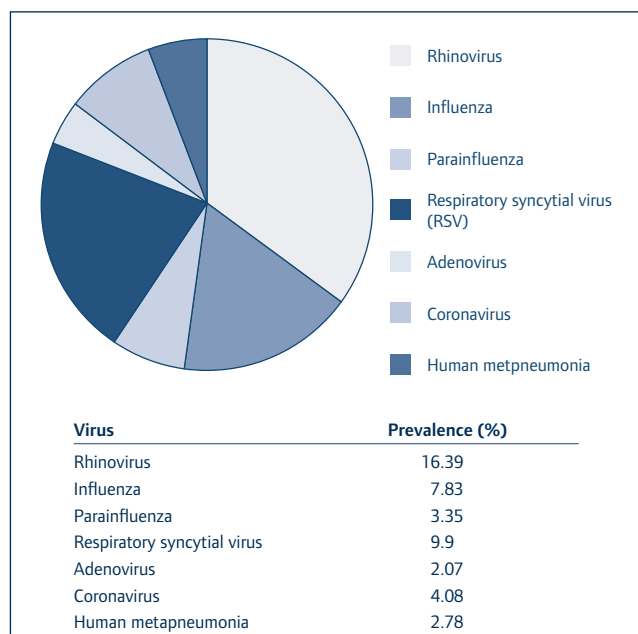


Figure 1. Relative prevalence of different respiratory viruses at exacerbation. Data adapted from [3]

Further circumstantial evidence derives from studies demonstrating the development of specific immune responses to viral pathogens following exacerbation [1].

While this evidence implicates respiratory viruses in the majority of naturally occurring exacerbations, it does not formally demonstrate causality. Studying patients with mild COPD, Mallia et al. produced the first human experimental model of COPD exacerbation. They used a small inoculum of rhinovirus to infect subjects who duly went on to develop clinically and pathophysiologically validated, but mild, exacerbations [4]. This model overcomes the difficulties inherent in studying naturally occurring exacerbations and provides a mechanism to study the separate roles of bacteria and viruses at exacerbation.

It has been proposed that viral infection may modulate host immunity to secondary bacterial infection. The long-recognised phenomenon that bacterial pneumonia may follow an episode of influenza may be one example of this [5]. It has been difficult to unpick this problem at exacerbation because, although bacteria and viruses can both be detected in the sputum, it is impossible to know the temporal relationship of the two, or to distinguish a causal versus bystander role. Experimental models of rhinovirus-

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induced exacerbations have allowed this to be studied in a much more detailed way. When experimentally infected with rhinovirus, the sputum of the subject becomes positive for bacteria in 60% of cases. The peak sputum viral load precedes the peak bacterial load by 6–10 days [6]. The implication is that many of the exacerbations previously attributed to bacteria may in fact be precipitated by a virus long disappeared from sputum at presentation.

Although this result challenges the orthodoxy on exacerbations, a second paradigm shift has been precipitated by new 16S rRNA-based bacterial detection methods that are far superior in sensitivity to traditional culture-based techniques. A detailed characterisation of the bacterial community in the lungs can now be produced, resulting in the view that the lower respiratory tract is not a sterile environment, but instead one colonised by a thriving microbiota – a concept more familiar in the gut. A prevalent theory of inflammatory bowel disease is that it results from a selfish outgrowth in particular residents of the gut microbiota [7]. The possible parallels with chronic lung disease are immediately apparent. In support of this, distinct microbiota do seem to exist in stable COPD compared to non-obstructed smokers and non-smokers [8]. Thus, the modern view would be that the distinction between health and disease is reflected by differences in bacterial populations within the airway microbiome, with further differences occurring in diseases such as COPD between the stable state and exacerbation.

Extending this view, Mallia et al. characterised the respiratory microbiota throughout the course of experimentally induced COPD exacerbations. Using samples of the subjects' sputum, they constructed a detailed phylogenetic tree before, and at several time points after experimental rhinovirus infection. They showed a significant increase in total bacterial load and an outgrowth specifically of *Haemophilus influenzae* in the COPD group (but not in the non-obstructed group) [9]. This leaves us in no doubt that acute viral infections can cause COPD exacerbations; however, the underlying mechanism is subtle, involving interactions between the virus, the immune system and the resident bacterial community.

In addition to a role in exacerbation, there are also data supporting a role of viruses in the progression of stable COPD. Smoking is the key environmental driver of COPD. All smokers develop a degree of airway inflammation [10]; however, only 10–15% will ultimately develop COPD [11]. This observation has mandated a search for other aetiological co-factors. Because chronically obstructed lungs harbour CD8+ cytotoxic T cells, their prevalence correlating with the degree of airway remodelling [12], chronic viral infection has been put in the research spotlight. HIV, chronic hepatitis C (HCV) and latent adenoviral infection have all been implicated.

Latency is a strategy deployed by a number of viruses, most notably those of the herpes virus family, to persist in the host. Childhood respiratory infection is an independent risk factor for development of adult COPD [13]. Adenoviruses cause a number of childhood respiratory infections including bronchiolitis. Because they are known to establish latency in the epithelial cells of the lungs [14], latent adenoviral infection has been proposed as the mechanism of this risk factor. Latent expression of the adenoviral E1A gene (a transcription activator) in epithelial cells is hypothesised to modify the inflammatory response to cigarette smoke. Tissue samples acquired during resection of lung tumours show a ubiquitous presence of E1A DNA [14] in the epithelial cells of smokers' lungs. The gene is present at three-times higher levels in patients with COPD [14]. In vitro studies of lung

epithelial cells expressing E1A have shown they produce higher levels of interleukin-8 and ICAM-1 when stressed with inflammatory stimuli [15,16]. Both IL-8 and ICAM-1 are involved in neutrophilic inflammation – the predominate form of inflammation seen in COPD.

However, doubts have been cast on the importance of latent adenoviral infection. McManus [17] used PCR to detect the adenovirus 5 E1A and adenovirus hexon genes (expressed in acute infection) in the sputum of COPD patients variously exacerbated or stable. Of the 171 patients tested, 13 patients had acute adenovirus 5 infection but only one had a PCR profile consistent with latent infection. The role of latent adenoviral infection remains unclear. It is interesting, however, to note that the same group, using the same study design, found Epstein-Barr virus present in 48% of exacerbations and 46% of stable patients and behaving very much like a latent infection [18].

The importance of blood-borne viruses in the lung-function decline in COPD is also debated. Patients with chronic HCV infection and comorbid COPD may have an accelerated pace of respiratory deterioration. This deleterious effect of HCV on lung function may be modulated by effective antiviral therapy [19]. As well as being an interesting research observation, this comorbid state is of clinical significance as levels of HCV infection are substantially higher in patients with COPD than the background population [20].

A similar finding is that people with HIV infection appear to be more susceptible to smoking-induced lung damage even when carefully controlling for drug use. Significantly higher levels of computed tomography-diagnosed emphysema have been observed in patients with HIV compared to HIV-negative controls [21]. Again mirroring the picture with HCV, patients with HIV are 50–60% more likely to have COPD than HIV-negative controls [22]. With HIV now best considered a long-term condition, appropriate management of comorbidities, especially those affecting, and affected by HIV, becomes increasingly clinically important.

It therefore appears that a disparate group of viruses may be involved in COPD disease progression. It is still unclear what may be common to these viruses that implicates them in this process, or whether multiple mechanisms are at play. Clearly further work is needed.

In summary, it is clear that viruses are responsible for a proportion of exacerbations, and there are emerging data that chronic viral infection may drive COPD disease progression. What unites these two features is our inability to effectively diagnose, and manage the role of viruses in COPD with effective antiviral medication. Until we do that, the clinical unmet need remains large. We are failing our patients. Respiratory medicine needs your help.

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