European Journal of Microbiology and Immunology 2 (2012) 3, pp. 176–185
DOI: 10.1556/EuJMI.2.2012.3.2

THE INFLUENCE OF VIRUS INFECTIONS ON THE COURSE OF COPD

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Received: May 7, 2012; Accepted: May 8, 2012

Chronic obstructive pulmonary disease (COPD) is extensively influenced by viral infections. The mechanisms of how viral agents affect the pathogenesis and prognosis of COPD are numerous. In general, patients with infectious exacerbations are characterized by longer hospitalization periods and greater impairment of several lung function parameters than those with non-infectious exacerbations. Prodromal, clinical, and outcome parameters fail to distinguish virally from non-virally induced illnesses in cases of exacerbations. The importance of infections with respiratory and non-respiratory viral agents for pathogenesis and course of COPD is detailed. Human adenovirus, non-respiratory viruses including human immunodeficiency virus, human metapneumovirus, influenza virus, human rhinovirus, and respiratory syncytial virus are especially stressed.

Keywords: chronic obstructive pulmonary disease, COPD, virus, infection, human adenovirus, human metapneumovirus, influenza virus, human rhinovirus, respiratory syncytial virus

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are worldwide a major cause of morbidity, mortality, and health care costs as well as decreased quality of life for the individual patient [1]. They are thought to be caused by complex interactions between the host's individual microbiome, bacteria, viruses, and environmental influences. These factors increase the inflammatory burden in the lower airways, overwhelming the protective anti-inflammatory defense mechanisms and thus leading to tissue damage. Frequent exacerbations are associated with increased morbidity and mortality, a faster decline in lung function, and a poorer general state of health [2].

Respiratory viral infections target the epithelial cells of the lung and lead to desquamation, microvascular dilatation, edema, and inflammatory cell infiltrate. These changes predispose the lower airways to bacterial infections, because they interfere with mucociliary clearance and reduce the bacterial clearance due to macrophages [3, 4] *(Table 1)*. Predominance of viral or bacterial infections is neither associated with the severity of exacerbation nor with the stage of COPD. Nevertheless, viral exacerbations are associated with a higher duration of hospital stay (average 9 days) than bacterial exacerbations (average 7 days) [5].

Viral infections are the most important causes and very common in COPD exacerbations [6–12]. In half [13, 14] to two-thirds of exacerbations, viruses are the causative pathogens. Combined bacterial and viral infection can be identified in 25% of exacerbations, and these dual infections are often more severe [1], although this increased severity is not confirmed by all studies [4]. Neither clinical nor biological markers, e.g. procalcitonin and C-reactive protein (CRP), can reliably distinguish between virus induced exacerbation and exacerbation due to other causes [13–15], though interleukin-6 (IL-6) is significantly increased and negatively

Table 1. Effects of respiratory viral infections in COPD

– Desquamation of epithelial cells
– Microvascular dilatation
– Edema
– Inflammatory cell infiltrate, especially CD-8 T-lymphocytes
– Reduction of mucociliary clearance
– Reduction of bacterial killing by macrophages
– Association with bacterial infections of the lower airways
– Induction of hyperinflammation that contributes to disease progression

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ISSN 2062-509X / $ 20.00 © 2012 Akadémiai Kiadó, Budapest

correlated to FEV-1 (forced expiratory volume within 1 s) in virus-induced exacerbations, indicating a relation between virus-induced inflammation and airway obstruction [16].

While single virus species are frequently detectable in stable COPD patients, detection of more than one virus species is usually associated with exacerbations. In general, viruses are more commonly detectable in patients with more severe airways disease [17]. Further optimization of vaccination and antiviral treatment might increase the prognosis of individuals with chronic respiratory disease [18].

Host response to viral infections is dysregulated in COPD [19]. Both respiratory viruses and non-infectious pathological processes in the lungs of humans with COPD were shown to activate the innate immune axis. They lead to increased numbers of invariant natural killer T-cells (iNKT-cells) and alternatively activated IL-13-producing macrophages in the lung [20]. Exposure to cigarette smoke induces alterations in the innate immune response to viral infection. These changes hasten alveolar destruction – that is typical for emphysema – at least in the mouse model [21]. In concert with this finding, viruses cause more severe disease exacerbation, heightened inflammatory response, accelerated loss of lung function, as well as increased symptomatology and mortality in smoking COPD patients compared with other causes of exacerbation of COPD.

Additionally, cigarette smoke enhances parenchymal and airway inflammation, as well as apoptosis, emphysema, and airway fibrosis. These processes are induced by the viral pathogen-associated molecular pattern (PAMP) poly(I:C) resulting in early induction of type I interferon (IFN) and IL-18, later induction of IL-12/IL-23 p40 and IFN-γ, the activation of the double-stranded RNA-dependent protein kinase (PKR), as well as the eukaryotic initiation factor-2α (eIF2α). Toll-like receptor 3 (TLR3)-dependent and -independent pathways as well as pathways that are dependent on the mitochondrial antiviral signaling protein (MAVS), interleukin-18 receptor α (IL-18Rα), IFN-γ, and PKR are involved [22].

The following review demonstrates the importance of respiratory and non-respiratory viral agents for the pathogenesis and course of COPD with special emphasis on human adenovirus (HAdV), human coronavirus (HCoV), non-respiratory viruses, human metapneumovirus (HMPV), influenza virus (IFV), human rhinovirus (HRV), and respiratory syncytial virus (RSV) *(Table 2)*.

Table 2. Common viruses with the potential to aggravate COPD disease

– Human adenovirus (HAdV)
– Human coronavirus (HCoV)
– Human metapneumovirus (HMPV)
– Influenza virus (IFV)
– Human parainfluenza virus (HPIV)
– Human rhinovirus (HRV)/picornavirus (PV)
– Respiratory syncytial virus (RSV)

Human adenovirus (HAdV)

Latent HAdV infections play an important role in the pathogenesis of COPD [23]. Double-stranded DNA viruses like HAdV are able to persist in epithelial airway cells long after the acute infection has been cleared. The E1A region of the adenoviral genome and the adenoviral E1A protein remain stable in these cells. During such latent infections, viral genes are expressed at the protein level without replication of complete virions [3]. E1A protein can be detected more often in patients with COPD than in healthy subjects [23]. The E1A region of adenoviruses was found in epithelial cells of 27% of COPD and chronic bronchitis patients, but not in patients with asthma and normal volunteers in China. Furthermore, E1A DNA was detected in 50% of COPD patients but only in 8% of patients with chronic bronchitis [24]. Newer data suggest that adenovirus E1A DNA is merely infrequently detectable in respiratory secretions from patients with COPD. Adenovirus can be detected with similar frequencies in exacerbated and clinically stable COPD patients [25].

The expression of the adenoviral trans-activating protein is associated with an amplification of the cigarette smoke-induced inflammatory response [3, 26]. The infection leads to independent increases in the number of CD8 cells, whereas cigarette smoke leads to higher numbers of CD4 cells in the inflammatory infiltrate. A latent infection with adenoviral agents also causes steroid resistance of the eosinophilic component of an allergic inflammatory response [3].

Adenoviral E1A transfection transforms primary human bronchial epithelial (HBE) cells and up-regulates their production of mediators that are clinically relevant to the pathogenesis of COPD. The E1A protein alters the expression of growth factors. Connective tissue growth factor (CTGF) as well as transforming growth factor β1 (TGF-β1)-mRNA and protein expression are up-regulated in E1A-positive HBE cells. *In vitro* experiments demonstrated that up-regulation of CTGF is independent of TGF-β secretion into the growth medium. Both, E1A-positive and E1A-negative HBE cells contain cytokeratin, but only E1A-positive cells express the mesenchymal markers vimentin and α-smooth muscle actin. Latent infection of epithelial cells by adenovirus E1A contributes to airway remodelling in COPD. The viral E1A protein induces TGF-β1 and CTGF expression, and shifts cells to a more mesenchymal phenotype [27, 28].

Lipopolysaccharide (LPS) stimulation of E1A-transfected HBE cells *in vitro* increases intercellular adhesion molecule-1 (ICAM-1) as well as interleukin-8 (IL-8) mRNA and protein expression compared with control cells. It also induces higher ICAM-1 promoter activity and higher nuclear factor-ϰB (NFκB) binding activity of nuclear extracts in E1A transfectants than in controls [27].

However, even E1A gene expression by itself enhances the soluble ICAM-1 expression and the recruitment of inflammatory cells into airways of COPD lungs, and leads to

Table 3. Effects of adenoviral infections in COPD patients

– Increase of CD-8 T-helper cells in the inflammatory infiltrate of the lung
– Induction of connective tissue growth factor and transforming growth factor β1 in human bronchial epithelial cells
– Induction of the mesenchymal markers vimentin and α-smooth muscle actin in human bronchial epithelial cells
– Increased susceptibility of intracellular adhesion molecule 1, interleukin-8, and greater nuclear factor-ϰB binding activity in infected cells in reaction to inflammatory stimuli
– Enhancement of the soluble intracellular adhesion molecule 1

an excess production of IL-8 by lung epithelial cells [26] *(Table 3).*

Persistence of an adenoviral infection is described as a possible cause of non-remitting airway obstruction in children. However, chronic obstructive bronchitis with inadequate response to inhaled steroid and bronchodilator therapy is a rather rare disorder in this age group [29]. Nevertheless, adenoviral infection might act as a starter of chronic obstructive bronchitis in children [29]. Childhood infection of the respiratory tract with adenoviral agents represents an independent risk factor for the pathogenesis of COPD in cigarette smokers [26, 30].

Human bocavirus (HBoV)

A major role of HBoV infections in adults with acute exacerbations of COPD is unlikely. HBoV is merely infrequently isolated from upper and lower respiratory tract specimens of COPD patients irrespective of the presence or absence of exacerbations [31].

Human coronaviruses (HCoV)

HCoV, in particular HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, were shown to trigger acute respiratory illness in elderly adults with COPD. Although HCoV infections in COPD patients are usually less severe than influenza infections, they can be associated with multiple respiratory and systemic symptoms as well as hospitalization [32] *(Table 2).*

Herpes group viruses, hepatitis B and C viruses, and HIV

Even non-respiratory viruses like Epstein–Barr virus (EBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) affect negatively the course of COPD. Latent infections seem to play an undeniable role in the pathogenesis of the disease.

EBV is associated with both pulmonary fibrosis and COPD. EBV DNA is more frequently identified in the respiratory tract of COPD patients in comparison to non-affected smokers [33]. Smokers without symptoms of COPD rarely have EBV in their sputum. The virus is present not only in exacerbations but also in times of stable disease, suggesting that the infection is persistent. EBV can be detected in nearly 50% of patients with COPD, while it can be demonstrated in the respiratory tract of less than 10% of non-obstructive smokers. Smokers, who are infected with EBV, are at increased risk for the development of COPD [33].

One case of a Herpes simplex virus type 1 (HSV-1) tracheobronchitis in a non-immuno-suppressed individual with repeated exacerbations of COPD, which did not respond to conventional treatment, has been described. As expected, the disease responded well to acyclovir-based therapy [34].

While liver diseases are associated with a high prevalence of COPD in general, hepatitis virus infections in particular show only a non-significant tendency towards an association with COPD [35]. Prolonged applications of high doses of systemic corticosteroids in addition to inhalative corticosteroids were demonstrated to increase the risk of hepatitis B virus (HBV) reactivation [36].

Chronic HCV infection seems to accelerate the worsening of lung function in COPD patients [37]. HCV-positive patients show a lower FEV-1 and a higher BODE-index than HCV-negative individuals [38]. Even a consequent therapy with interferon-α cannot stop the decline of FEV-1 [37]. Prevalence of chronic HCV infection is increased in COPD patients in comparison with healthy blood donors [38].

HIV is a risk factor for the development or progression of COPD. Infection with HIV is associated with COPD, accelerated emphysema development, chronic bronchitis, small airways abnormalities, and non-specific airway hyper-responsiveness [39]. Respiratory symptoms including dyspnea, cough, and phlegm production are, with more than 40% each, extremely common in HIV-seropositive (HIV+) individuals. These patients are at increased risk for the development of respiratory symptoms even prior to the onset of acquired immunodeficiency syndrome (AIDS)-related pulmonary complications [40]. They commonly show a reduced pulmonary diffusion capacity (DLCO). HIV+ patients with diffusion impairment demonstrate prominent reductions in capillary blood volume (V_c), despite a well-preserved total lung capacity (TLC), no evidence of interstitial fibrosis, but evidence of early emphysema that significantly correlates with DLCO [41].

Table 4. Effects of HIV infection on the course of COPD

– Regular occurrence of cough, dyspnea and phlegm production
– Reduction in pulmonary diffusion capacity
– Reductions in capillary blood volume
– Early emphysema
– Heightened susceptibility to cigarette smoke
– Increased numbers of cytotoxic lymphocytes

Current or prior cigarette smoking is the most important predictor of respiratory symptoms, but the susceptibility to the effects of cigarette smoke is heightened in HIV+ patients with COPD [40]. Moderate dyspnea was shown to be significantly increased in HIV+ COPD patients [42]. The HIV-triggered acceleration of the onset of smoking-induced emphysema [43, 44] could be an effect of cytotoxic lymphocytes, whose count is increased in HIV+ individuals with emphysema [44] *(Table 4)*. Concordantly, the use of the antiretroviral agent lamivudine is associated with a significant reduction of dyspnea [40].

Human metapneumovirus (HMPV)

HMPV infects virtually all children by the ages of 5–10 years. The pathogen may contribute to exacerbation of COPD [45, 46] and was shown to lead to serious sequelae in COPD patients [47]. It should be considered as a possible viral trigger of acute exacerbations because asymptomatic carriage is unlikely [48]. However, the virus is only detectable in a very small number of patients with acute exacerbations of COPD [45, 48]. Nevertheless, in these rare cases, prolonged morbidity and hospital stay, as well as increased mortality, have been described, particularly in the elderly. Pneumonia, hypoxemic, or global respiratory failure requiring mechanical ventilation and lymphopenia have been described [49].

In addition, HMPV infections predispose to bacterial pneumonia. Co-infection with respiratory syncytial virus (RSV) leads to increased severity of clinical disease [46].

Influenza virus (IFV)

IFV infection causes excess morbidity and mortality in COPD patients [50]. Vice versa, COPD is a risk factor for particularly severe courses of influenza A(H1N1)pdm09 infections [51].

Influenza infection can lead to exacerbations resulting in a reduced quality of life, hospitalization, and even death in the most severe cases [52]. The virus primarily infects the respiratory tract and can lead to fulminant primary viral and secondary bacterial pneumonia [53].

Cigarette smoke may play an important etiological role in 'topical' immunosuppression, as cigarette smoke extract (CSE) inhibits influenza-induced IFN-inducible-protein-10 protein and mRNA expression, major antiviral cytokine IFN-β mRNA expression, and viral-mediated retinoic acid inducible gene I (RIG-I) mRNA and protein expression. The latter is believed to be of importance for the recognition of, and response to, RNA viruses like influenza virus. Its suppression can be prevented by *N*-acetyl-cysteine and glutathione [54]. In smoke-exposed mice, IFV infection is associated with increased expression of the CC-chemokine receptor chemokines: monocyte chemotactic protein (MCP)-1 and -3, as well as the CXC-chemokine receptor chemokines: keratinocyte chemoattractant (KC), macrophage inflammatory protein-2 (MIP-2), and granulocyte chemotactic protein-2 (GCP-2) in comparison to control mice [55].

Upon infection, two antigens are present on the viral surface of IFV: hemagglutinin and neuraminidase that play a crucial role for the induction of human IFV immunity. Since many varying alleles of these antigens appear due to antigenic drift, immunity in the population is blunted [56]. Annual anti-influenza vaccination is therefore recommended for patients with COPD [50]. It reduces the rate and severity of COPD exacerbations and slows down the disease progression in this way [57]. Information campaigns to gain attention of risk groups like COPD patients are advisable, particularly in epidemics [58].

The vaccine that usually consists of a cocktail of three strains must be annually updated due to the continuous antigenic changes of IFV. Inactivated influenza vaccines have been used for over 50 years and have an excellent safety record [52]. Influenza vaccination is associated with only minimal local adverse reactions. It usually does not cause systemic adverse reactions, neither clinical exacerbations nor adversely affection of lung function, regardless of the severity of airflow obstruction [59]. Trivalent inactivated influenza virus vaccine (TVV) and trivalent live cold-adapted influenza virus vaccine (CAIV-T) are likely to stimulate protective immune responses. TVV combined with CAIV-T are more immunogenic than TVV alone [60]. Receipt of cold-adapted influenza virus vaccine is associated with temporary stabilization of COPD, while acute respiratory illness is associated with a worsening concerning functional status and subjective well-being [61]. Seasonal influenza vaccination of patients with severe COPD with trivalent influenza split virion vaccines leads to increases of anti-influenza (A and B) IgG levels and reduces hospitalization, pneumonia, and the need for intensive care treatment [62]. Intradermal vaccination with reduced doses may be considered in countries with restricted access to influenza vaccines due to considerable costs [63]. As an interesting side effect of seasonal influenza vaccination, induction of cross-neutralizing antibodies against H5N1 IFV was demonstrated in elderly COPD patients in Thailand [64].

Although influenza vaccination is highly effective in the prevention of influenza-related acute respiratory illnesses regardless of the severity of COPD, it does not prevent other acute respiratory illnesses that are unrelated to influenza. The effectiveness of influenza vaccination in the prevention of overall acute respiratory illnesses in patients with COPD depends on how much the proportion of influenza-related acute respiratory illnesses contributes to the incidence of total acute respiratory illnesses [65].

When started early, antiviral drugs, especially neuraminidase inhibitors, can be prescribed in adjunct to non-specific interventions in an attempt to shorten disease duration and to prevent complications in case of influenza infection. However, the effectiveness of antiviral drugs specifically in patients with COPD has not been proven so far [56].

Dexamethason leads to a reduction of chemokine levels but not of neutrophilia in smoke-exposed, IFV-infected mice, and is associated with a worsening of symptoms. However, treatment with peroxisome proliferator-activated receptor-γ (PPARG) agonists like pioglitazone shows promising effects in mice [55].

Human rhinovirus (HRV)

HRV, a member of the family *Picornaviridae*, is the causative pathogen in more than half of acute viral infections of the upper respiratory tract. The viruses are associated with acute exacerbations of respiratory disease, including asthma, sinusitis, otitis media, and COPD [66, 67]. In fact, they represent the most common infectious cause of chronic obstructive pulmonary disease exacerbations [68, 69]. Viral symptoms with high predictive value in COPD patients with picornavirus infection include rhinorrhea, sore-throat, and discrete IL-6 increase [70]. Cough is usually associated with increased production of neuropeptides and leukotrienes, altered expression of neural receptors, and increased airway mucus production [71].

HRV not only is a well-recognized cause of common colds, but is also able to induce illnesses in the lower respiratory tract [72]. The virus can be identified in nearly 20% of exacerbations of COPD [73]. This is typically associated with elevation of lower airway IL-6 levels, which may mediate lower airway symptoms during chronic obstructive pulmonary disease exacerbations [74]. In contrast, interferon production by bronchoalveolar cells of COPD-patients is impaired, being associated with higher virus loads than in patients without COPD [75].

Symptoms are more serious in cases of bacterial co-infections. Exacerbations with both HRV and *Haemophilus influenzae* are associated with higher bacterial loads and serum IL-6 levels than exacerbations with only one pathogen [73]. In exacerbations with both cold symptoms as a marker of putative viral infection and a bacterial pathogen, the decline of FEV-1 is greater and symptom count is higher than in those that are caused by a bacterial pathogen alone [73].

Frequent exacerbators experience significantly more colds than infrequent exacerbators. However, the likelihood of exacerbation during a cold is unaffected by exacerbation frequency. Exacerbation frequency in chronic obstructive pulmonary disease is associated with an increased frequency of acquiring common cold, rather than an increased propensity to exacerbation once a cold has been acquired. Patients experiencing frequent colds have a significantly higher exposure to cigarette smoke [76].

HRVs are capable of efficient replication after experimental infection *in vitro* at temperatures that are present in the tracheobronchial tree and cause productive infection, increased cytokine and chemokine levels, and up-regulation of cell surface markers in human bronchial epithelial cells [72]. The replication increases the expression of Toll-like receptor 3 (TLR3) mRNA and TLR3 protein on the cell surface of human bronchial epithelial cells. TLR3 is important for the mediation of the antiviral response [66]. CXCL10, also known as IFN-γ-inducible protein 10 (IP-10), plays a role in the pathogenesis of HRV-induced colds and in HRV-induced exacerbations of COPD [77, 78]. It can be induced by the infection of primary cultures of human airway epithelial cells or of human bronchial epithelial cells with rhinoviruses. IP-10 is a ligand for the CXCR3 receptor that can be found on activated type 1 T-lymphocytes and natural killer cells. Generation of IP-10 requires an intracellular virus capable of replication but is dependent on prior induction of type 1 interferons [77, 78]. Transfection of synthetic double-stranded RNA into epithelial cells induces robust production of IP-10, whereas transfection of single-stranded RNA has no effect. Induction of IP-10 gene expression by HRV-16 depends upon activation of NFκB, as well as other transcription factor recognition sequences further upstream in the IP-10 promoter. *In vivo* infection of human volunteers with HRV-16 strikingly increases IP-10 protein in nasal lavages during symptomatic colds. Levels of IP-10 correlate with symptom severity, viral titer, and numbers of lymphocytes in airway secretions [77, 78]. IP-10 is thus suited as a potential biomarker for rhinovirus-induced exacerbations of COPD [78, 79] *(Table 5).*

On the cellular level, elevated protein levels of IL-6, IL-8/CXCL8, and growth-related oncogene-α/CXCL1 are measurable after rhinovirus stimulation [80]. Rhinovirus-encoded proteinase 2A triggers *in vitro* activation of monocyte-derived dendritic cells and the induction of Th1 and Th2 immune responses from CD4 T-cells. In laboratory mice, intranasal installation of rhinovirus proteinase 2A leads to increased airway hyperreactivity, lung inflammation, and IL-4 and IFN-γ production from CD4 T-cells. Such alterations of immune response are believed to be associated with worsening of dyspnea and respiratory failure in COPD patients [81, 82]. Cigarette smoke extract differentially modulates rhinovirus-induced chemokine profiles in human airway epithelial cells. It increases a rhinovirus-induced stimulation of CXCL8 production via mRNA stabilization and inhibits rhinovirus-induced CXCL10 production via transcriptional regulation [83].

Safe and effective antiviral agents are desirable for both prevention and treatment of HRV infections in COPD patients [72]. An advanced antiviral agent against HRV in-

Table 5. Effects of rhinovirus in patients with COPD

– Increased lower airway interleukin-6 levels
– Additional worsening of FEV-1 values in COPD patients with bacterial infections
– Increased expression of Toll-like receptor 3 in human bronchial epithelial cells
– Induction of interferon-γ-inducible protein 10 (CXCL10/IP-10) after prior induction of type 1 interferons mediated by nuclear factor-κB

fections is pleconaril, a viral capsid-binding inhibitor with potent and highly specific *in vitro* activity against the majority of serotypes of rhino- and enteroviruses [67].

Respiratory syncytial virus (RSV)

RSV infection – a common cause of childhood bronchiolitis – is also an important illness in elderly and high-risk adults, with a disease burden similar to that of non-pandemic influenza A in a population in which the prevalence of vaccination for influenza is high [84]. RSV RNA can be identified by reverse transcriptase-polymerase chain reaction (RT-PCR) in a high percentage of COPD patients. Most RSV infections in patients with COPD are associated with symptomatic respiratory illnesses and measurable immune responses [85].

Symptoms are usually milder in adults than in children, but severe courses have been described. Viral shedding is usually low in adults, making diagnostics challenging and stressing the need for sensitive molecular tools. The therapeutic effects of ribavirin and palivizumab in the affected adult are yet poorly investigated. Only severely immunocompromised patients or patients with severe respiratory failure are regularly treated [86].

An effective RSV vaccine may offer benefits for these adults [84], because immunization would be presumably most effective. However, no effective vaccine is available yet [86, 87].

Increased susceptibility of COPD patients to RSV is believed to be due to RSV- or immune response-induced pulmonary effects that are altered by age, environmental exposures, genetics, COPD itself, or a combination of these [88]. RSV can lead to activation and recruitment of T-cells that amplify and skew the immune response towards more intense pathology, including mucus production and remodeling of the airways in COPD patients [89].

Despite contradictious reports [85], several studies suggest asymptomatic persistence of RSV in COPD with detections being as frequent in stable COPD patients as in patients with disease exacerbations. Contributing factors of a potential RSV persistence in COPD patients comprise impaired antiviral immunity due to cigarette smoke and COPD itself, induction of skewed type 2 T-helper cell responses by RSV with consecutive immune evasion, antagonizing antiviral cytokines, mimicking chemokines, inhibiting apoptosis, entering immune-privileged cells such as pulmonary neurons, and antigenic drift of the virus [90].

Discussion

Respiratory viruses represent both important triggers of acute exacerbations and 'key players' in COPD pathogenesis [91]. The infiltration of COPD airways with CD8+ T-cells gives hints suggesting that viral agents could influence the course of COPD [23, 25] *(Table 1).* Viral infections induce pro-inflammatory chemokine production [92]. Childhood respiratory infections are an independent risk factor for the subsequent development of COPD [93]. In patients with moderate or severe COPD, the presence of a virus in upper airway secretions is strongly associated with the development of COPD exacerbations. Viral respiratory tract infections are causally associated with both hospital and community associated exacerbations [94].

HRV, HCoV, IFV, RSV, parainfluenza virus (HPIV), HAdV, and HMPV are important viral causes of chronic obstructive pulmonary disease exacerbations *(Table 2).* These exacerbations can be severe with prolonged recovery times [68, 94]. However, viral infection does not appear to have effects on subsequent readmissions or mortality rate. Viral detection rates are independent from FEV-1 values in COPD patients [95]. Colonization of the lower respiratory tract with bacterial or viral infectious agents results in chronification of inflammatory processes and progress of COPD. Colonization correlates with the severity of the disease [96].

Some viruses, such as RSV, stimulate the helper T-lymphocyte type 2 (Th2)-pattern of immune responses that is associated with allergic inflammation. Other viruses, such as HAdV, appear to persist as latent infections in the airways of patients with COPD, and adenoviral E1A protein is capable of amplifying host genes, possibly including those involved in cigarette smoke-induced lung inflammation [93].

Bacterial exacerbations of COPD are also frequently associated with viral infections. More than 45% of exacerbation cases due to non-typeable *H. influenzae* are associated with evidence of acute co-existing viral infection [97]. More than 40% of the patients with COPD exacerbation requiring mechanical ventilation are infected with a viral pathogen. There is no statistically significant difference in prodromal, clinical characteristics or outcomes between the groups with and without viral infections [6]. However, patients with infectious exacerbations suffer from prolonged hospitalizations and greater impairment of several lung function parameters than those with non-infectious exacerbations. Airway neutrophilia is related to exacerbation severity regardless of viral and/or bacterial infections, while eosinophilia is a good predictor of viral exacerbations [98]. The values of sputum inflammatory markers are increased in COPD patients with symptoms of a common cold or detected HRV at exacerbation, thus suggesting that viral infections lead to greater airway inflammation and thus more severe exacerbations [99]. The expression of airway neutrophilic inflammation markers increases at the time of acute COPD exacerbation and then declines 1 month later. This acute inflammatory response appears to occur independently of a demonstrable viral or bacterial airway infection. Patients with documented infection do not demonstrate greater increases in sputum levels of inflammatory cytokines during exacerbations compared with patients without demonstrable infection. This effect can be demonstrated for myeloperoxidase (MPO), tumor necrosis factor-α (TNF-α), and IL-8 [100].

Increased plasma fibrinogen and IL-6 levels are further signs of systemic inflammatory effects during COPD exacerbations [99].

Picornavirus, coronavirus, and influenza virus are not the only common infectious agents associated with COPD infections, but RSV, influenza A and B, HPIV 3, HCoV, and picornavirus also can be detected by nested RT-PCR in upper and lower respiratory tract specimens [101]. These viruses are significantly more often detected in hospitalized COPD patients than in non-hospitalized ones. Induced sputum contains respiratory viruses more frequently and in higher concentrations than nasal lavage in COPD patients [102]. PCR is the most sensitive method for the detection of viral pathogens [6] *(Table 6).* One significant disadvantage of the technology is its lacking ability to differentiate infection from colonization [68].

According to a recent review, the weighted mean prevalence of respiratory viral infections in COPD exacerbations is 34%. Viral exacerbations are most frequently reported from Europe, followed by the USA, Australia, and Asia. Picornaviruses are leading in Western countries, influenza virus in Asia. The weighted mean prevalences for the respective viruses were 17.3% for picornavirus (7.2–27.3%), 7.4% for IFV (2.9–12.0%), 5.3% for RSV (1.6–9.0%), 3.1% for HCoV (0.4–5.8%), 2.6% for HPIV (0.4–4.8%), 1.1% for HAdV (0–3.3), and 0.7% for HMPV (0–1.8) *(Table 2)* [103]. The lower quantitative relevance of IFV in studies from Western countries might be attributed to considerably high vaccination rates of up to 87% [104].

According to Dimopoulos et al., the most common virus detections in COPD exacerbations comprised of RSV (subtypes A and B) (40.5%), IFV (subtypes A, B, and C) (11%), HRV (8%), and HPIV (subtypes A and B) (7.5%), while bacterial causes were identified in no more than 14% of the patients and combined bacterial/viral infections in 13% *(Table 2)* [5].

In contrast, a study by Seemungal and coworkers demonstrated that the most common respiratory viruses detected during COPD exacerbations are HRV (58.2%), non-respiratory syncytial virus (16%), and RSV (23.5%) *(Table 2).* The latter ones are often detected in stable COPD patients as described above. Viral exacerbations due to HRV are associated with frequent exacerbators, colds with increased dyspnea, a higher total symptom count at presentation, a longer median symptom recovery period of 13 days, and a tendency towards higher plasma fibrinogen and increased serum IL-6 levels. RSV detection is associated with higher inflammatory marker levels than the presence of non-respiratory syncytial virus [105].

Table 6. Detection methods of respiratory viral infections in COPD patients

– Nuclear acid sequenced based amplification in:
– Bronchoalveolar lavage
– Induced sputum
– Nasal lavage

The epithelial cell is the principal site of viral infection in the airways and plays a central role in viral modulation of airway inflammation by the release of a variety of cytokines, chemokines, and growth factors. The epithelium also contributes to the host's innate defense response to viral infection by releasing products that are antiviral and/or can lead to increased recruitment of dendritic cells and lymphocytes. Some evidence supports a role of the epithelial cell in specific immunity, although the response of more conventional cells of the immune system to viral infections is the dominant factor in this regard [106]. Antiviral defense depends at least in part on a network of mucosal epithelial cells and macrophages. When this network is compromised, the host is highly susceptible to infection, but network components can be engineered to provide increased resistance. Attempts to improve antiviral defense may also lead to permanent inflammatory airway disease long after the infection has been cleared [107] *(Table 1).* Development of *in vitro* experimental models of virus infection has identified IFN-β and nitric oxide (NO) as possible therapeutic targets to augment antiviral immunity, and NFκB as a target for development of anti-inflammatory therapies [108].

Little is known yet about the details how viral agents influence the pathogenesis of COPD, so there still remains a field of intensive research. Many of the cellular and molecular mechanisms by which viruses cause exacerbations are still undetermined. The use of biomarkers represents a potential diagnostic tool that could provide new insights into the pathogenesis of viral infections in COPD patients [68]. Current therapies are not very effective in the prevention or treatment of virus-induced exacerbations of COPD. Exacerbations are therefore a major unmet medical need [109]. A better understanding how viral infections support the progress of COPD could lead to new therapeutic approaches improving the outcome of exacerbations and the prognosis of COPD.

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